Data collection on risk factors in pregnancy

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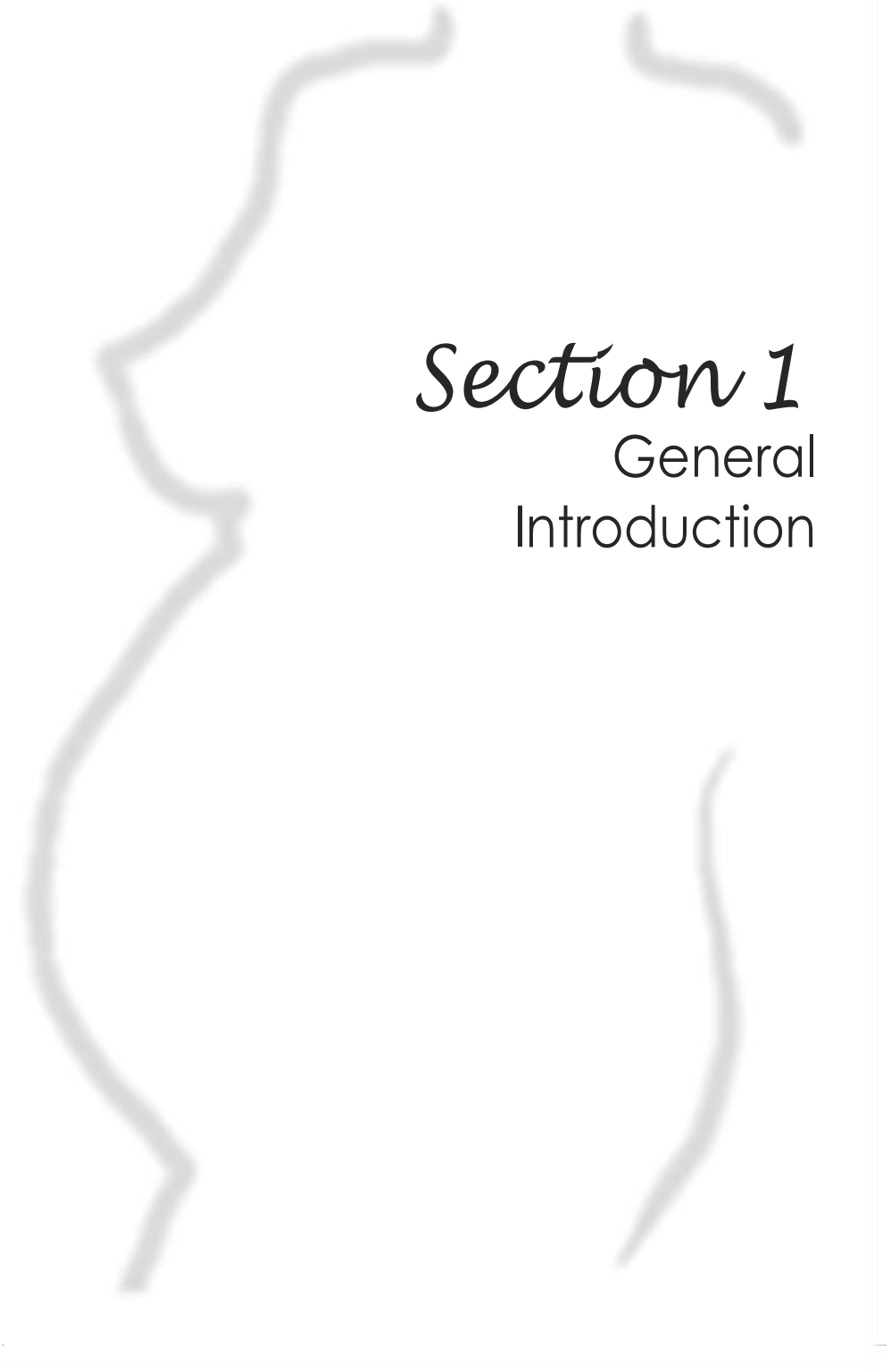
Table of contents



Section 1

General Introduction

Many pregnancies are carefully planned nowadays and generally, when a woman gets pregnant, she will do anything possible to protect the health of her yet unborn child. Not all negative birth outcomes can be prevented, but due to extensive research, more and more is known about risk factors and subsequent preventive actions in pregnancy. Yet in spite of this increasing knowledge many risks are still unclear and a lot is to be uncovered about the effects of certain health and lifestyle factors before and during pregnancy.

Epidemiologic research provides a substantial contribution to healthy pregnancies. The two main types of observational analytical epidemiological studies are the cohort study and the case-control study. Generally, a cohort study measures the occurrence of disease or outcome in two groups of individuals followed over a period of time (the cohorts), one exposed and one unexposed, allowing for direct measurement of incidence of outcome in both groups and examining multiple effects of a single exposure. In a case-control study participants are grouped based on the expression of the disease studied. The proportions exposed in both groups are compared. The advantage of a case-control design is its suitability for investigating relatively rare outcomes or outcomes with long latent periods, since participants have already developed the outcome, but it can only be performed retrospectively [1]. Both study-types have its variants, like the retrospective cohort study, the case-crossover study and the case-population design.

To be able to appoint negative or protective effects of health and lifestyle factors around pregnancy on the future health of the child, epidemiologic researchers ideally need complete and valid information about the widest possible range of pregnancy characteristics and detailed information on the outcome under investigation. These data can be obtained in various ways. Health care providers or medical records can be consulted retrospectively. This information was originally collected for medical reasons and data important for epidemiological research might be missing. Another approach is to form a pregnancy cohort. Women planning a pregnancy or being pregnant are asked to join the cohort and provide information about their pregnancy, lifestyle choices, health and medication use. This information prospectively provided by the women themselves can be complemented with data from health care providers, medical records or tissue samples.

Prospective data collection directly from pregnant women has several advantages. Since the pregnancy has not ended yet, women will remember their health and lifestyle choices and recall bias is avoided. Yet for a rare exposure to be associated with a rare outcome, large numbers of participants will be needed. There are several methods to collect direct prospective data from pregnant women. Traditionally pen-and-paper surveys are handed out or send to potential participants by mail. Another approach is to conduct an interview either face-to-face or by telephone.

The cost-effectiveness of these traditional modes has been a point of discussion. Distributing and collecting questionnaires or performing interviews is time consuming and expensive and recruitment rates are declining over the years.

Ever since the Internet is emerging, researchers have been investigating its possibilities as a tool for data collection. A Web-based survey is convenient for participants, data collection is efficient, direct entry of the data in the database assures data quality and many potentially eligible subjects are to be reached [2,3]. Internet access is still increasing and although literature shows that respondents attending a web-based survey are comparable to the ones participating in traditional survey methods and information acquired is at least as reliable, researchers are still debating the validity of the data collected and the selectivity of the sample acquired [2,4-6].

To explore the possibilities of collecting information on medication use and other potential risk factors directly from pregnant women via the Internet, the PROTECT pregnancy study has been set up. Pregnant women were recruited in four participating countries: The United Kingdom (UK), Denmark, The Netherlands and Poland. After enrolment women were to complete a baseline questionnaire to provide demographic information, information about their health and lifestyle, their pregnancy and medication use just before and during this pregnancy. On a periodic basis participants were asked to give an update of this information, and when the pregnancy had ended women were asked to fill in a short questionnaire about the pregnancy outcome. The design of the study is shown in Appendix 1.

This thesis aims to investigate the different methods of data collection of risk factors in pregnancy. In addition several observational epidemiologic study designs were used to assess associations with negative birth outcomes. The benefits and drawbacks of the use of the Internet for data collection were elaborated, along with those of more traditional methods and direct data collection from the pregnant women themselves is compared to indirect data collection from existing databases. The databases used for the studies in this thesis are the IADB.nl pregnancy database and EUROCAT NNL.

EUROCAT NNL is a population-based birth defect registry in the northern part of the Netherlands, covering approximately 10% of all births in the country. All livebirths, stillbirths and terminations of pregnancy affected with a major malformation of which the mother lived in the EUROCAT region at the time of birth can be recorded in the database. Regional obstetricians and physicians are asked to report birth defects and in addition eligible cases are actively traced in hospital reports. Information about the malformations present and about possible risk factors is collected from the parents, hospital records and pharmacies.

The IADB.nl is a population-based pharmacy prescription database containing data on prescriptions filled at 55 pharmacies in the Northern Netherlands, covering a population of approximately 500,000 individuals.

Because of the high level of commitment of patients to their pharmacies, the IADB.nl contains an almost-complete medication history for each individual registered, except for medications prescribed during hospitalization or bought over-the-counter. The IADB.nl has established a pregnancy database by connecting every child registered in the database with a female, 15–50 years old, with the same address code, providing there is only one. Using this method, the pregnancy period can be identified for the mother by subtracting 273 days (3 trimesters of 91 days) from the child's date of birth.

One of the area's in which there is still a lack of information about possible effects on the fetus is the use of medications during pregnancy. Many pregnant women use medications during pregnancy. Drug use during pregnancy cannot always be avoided, especially for women with chronic conditions. And since the first weeks of pregnancy are the most critical for the developing embryo, possible negative effects have already taken place when a pregnancy is identified and actions are taken. A literature review reported estimates of overall prescription drug use in pregnancy in developed countries of 27-93% (excl. vitamins and minerals) [7]. For many drugs on the market, the effects on the unborn child still have to be established. Since results from animal studies do not always predict teratogenicity in humans and pregnant women are excluded from pre-marketing trials for ethical reasons, post-marketing surveillance is necessary. Therefore, one of the focal points of this thesis is the collection of data on medication use during pregnancy and the investigation of relations between the use of particular medications during pregnancy and several negative effects for the child.

Another focal point is the use of folic acid supplements before and during pregnancy. The use of folic acid before and during pregnancy to prevent neural tube defects (NTDs) are known for quite a while now [8,9] and ever since other benefits have been discovered [10,11] . Yet, the use of folic acid in Europe can still be improved. Unlike USA, Canada and other countries, most European countries did not yet introduce mandatory fortification of food with folic acid and periconceptional supplementation of folic acid in several European countries showed to vary from 7-51% [12,13]. On the other hand, there has always been discussion about the safe upper limit of folic acid supplementation. Folic acid use has been linked to the development of cancer although findings were contradictory, and there have been concerns about the long term health effects for the offspring [14-18].

Besides evaluating folic acid as a supplement to promote the health of the baby we will also focus on asthma and the use of asthma medication during pregnancy as potential risk factors for the baby's health. Asthma prevalence has increased worldwide, with estimates up to 12% of pregnant women having asthma [19.20]. While negative effects of asthma medication on the unborn child have shown to be minimal [21], uncontrolled asthma during pregnancy is associated with significant risks for the mother as well as the baby [22,23].

Therefore, current international guidelines on the treatment of asthma recommend optimal asthma control during pregnancy [24,25]. In this thesis we will use different methods to investigate the use of asthma medication before and during pregnancy.

Contents of this thesis

The next section of this thesis will cover direct data collection via pen-and-paper questionnaires. Chapter 2.1 describes a survey conducted in 2009 among pregnant women in the Northern Netherlands at their knowledge and use of folic acid. Chapter 2.2 shows the results of a follow-up survey conducted five years later. Chapter 2.3 describes a comparison study evaluating the representativeness of a Dutch non-malformed control group to see if it is useful as a control-group for EUROCAT NNL.

Section three of the thesis is about indirect data collection and the studies outlined in this section all use the IADB.nl or EUROCAT NNL database. Chapter 3.1 shows the results of a drug-utilization study, describing the use of asthma medication around pregnancy using the IADB.nl pregnancy database. In Chapter 3.2 the IADB.nl pregnancy database is used in a cohort study to investigate the association of high dose folic acid use in pregnancy with the use of asthma medication in the offspring. Chapter 3.3 consists of a case-control study using EUROCAT NNL data to assess the association of folic acid antagonists with folic acid sensitive birth defects. Section three ends with a case-population study investigating whether a comparison of drug use rates in case pregnancies from EUROCAT NNL with population based prescription rates from the IADB.nl, could be used to detect signals of teratogenic risk of drugs (Chapter 3.4).

Section four describes data collection in pregnancy using web-based questionnaires and starts with an introductory chapter (Chapter 4.1) showing the results of a review investigating the use of web-based surveys examining a pregnancy-related topic. Benefits and drawbacks are evaluated, along with the topics covered, and validity and completeness of the web-based surveys compared to traditional methods. The study shown in Chapter 4.2 compares data about lifestyle factors and birth outcomes entered by the women participating in the PROTECT pregnancy study with figures of pregnant women in the general population of the participating countries to explore representativeness of the sample and validity and completeness of the data collected. Chapter 4.3 describes a survey with pregnant women having asthma asking about their medication use, the course of their condition during pregnancy and their perceptions about the risks of their asthma and asthma medications for their baby.

Finally the thesis concludes with a general discussion of our findings, practical implications and recommendations for further research.

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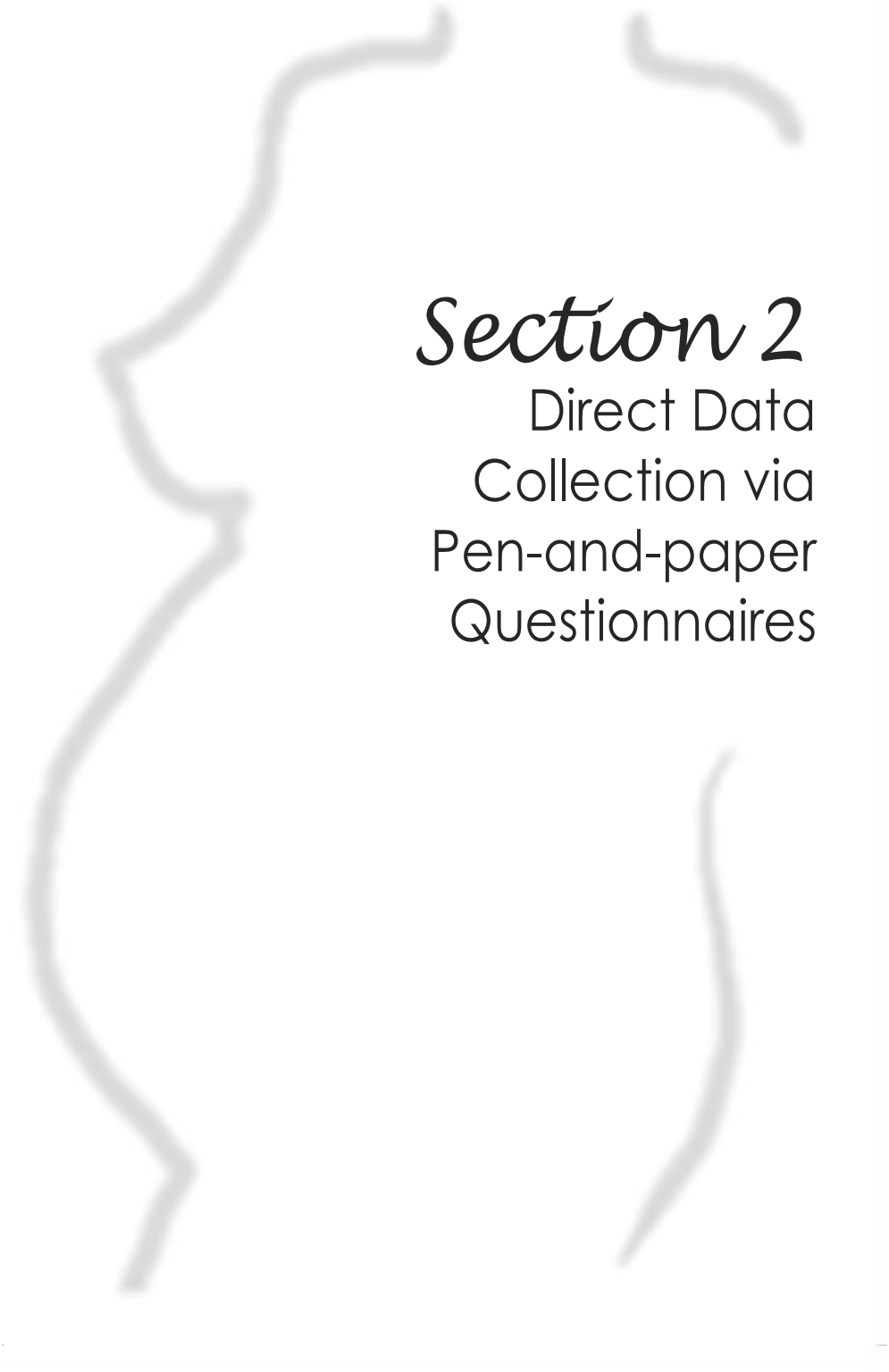

Section 2

Direct Data Collection via Pen-and-paper Questionnaires

Chapter 2.1

Periconceptional folic acid use: Still room to improve.

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Abstract

Background

Folic acid use before and during pregnancy prevents neural tube defects (NTDs). Since 1995, six surveys have been carried out among pregnant women to measure their knowledge and use of folic acid. The results of the most recent survey (2009) will be discussed and compared with earlier surveys.

Methods

Pregnant women in the Northern Netherlands were asked to fill out a questionnaire when visiting their midwife or gynaecologist.

Results

Of all 515 participating women, 87.0% heard about folic acid before they became pregnant. Of all respondents, 51.6% reported to have used folic acid during the entire recommended period. Multivariate analysis showed that planned pregnancy (OR 7.1 95% CI 2.4-20.7), smoking (OR 0.2 95% CI 0.7-0.7), folic acid use during a former pregnancy (OR 22.6 95% CI 5.5-92.8) and the number of previous children (per child: OR 0.5 95% CI 0.3-0.9), were predicting factors for the recommended use of folic acid. 89.9% of women were knowledgeable to start to use folic acid before pregnancy.

Conclusion

The knowledge about folic acid has declined over recent years and the use during the recommended period did not improve since the survey of 2005. Based on this survey there is still room for improvement with respect to knowledge and actual use of folic acid before pregnancy. Attention to these aspects should focus on younger, low-educated women, and should include information about family planning and contraceptives.

Introduction

Although the benefits of the use of folic acid before and during pregnancy to prevent neural tube defects (NTDs) are known for quite a while now [1,2], the use of folic acid in Europe can still be improved. Unlike USA, Canada and other countries, most European countries did not yet introduce mandatory fortification of food with folic acid. A recent review [3] showed that periconceptional use of folic acid in several European countries varies from 7-48%. EUROCAT, a network of population based registers of congenital abnormalities in Europe, presented figures of folic acid use in its report, varying from 1% of periconceptional folic acid use in France to almost 50 % in Norway and the UK [4]. In the Netherlands, about 120 children a year (6 per 10.000) are born with an NTD. The importance of periconceptional folic acid use is well-known, but what is the actual use of folic acid by women who planned to get pregnant and during pregnancy?

Since the first recommendations regarding folic acid in 1993, several interventions have been undertaken to increase the use of folic acid among women who plan to get pregnant. These interventions have been evaluated in the northern Netherlands in earlier reports [5-9]. De Walle et al found that socioeconomic status of a woman, measured by her highest level of education, is an important predictor of the recommended use of folic acid (400 mcg, starting 4 weeks before conception up until 8 weeks after) [9].

It is important to follow the development of folic acid use to evaluate the efficiency of the interventions taken. Since 1995, six surveys had been carried out among pregnant women to measure their knowledge and use of folic acid. A new survey was performed in early 2009 and the results are discussed in this article.

Methods

We approached the same 7 midwifery practices and 3 gynecological departments of hospitals in the northern Netherlands as we did for the 6 previous surveys [9]. One of the practices was unable to participate, so we distributed these questionnaires among the other practices. Pregnant women who were consulting the practice were asked to fill out a questionnaire. This standardized questionnaire had also been used in the previous surveys. There were some minor changes in the questions, but the questionnaire was still valid. Pregnant women were asked about their current and former pregnancies, about alcohol use, smoking and medication use in the three months before pregnancy, if they had ever heard about folic acid, what they knew about it (why use it and what period), and how they got this knowledge.

The participants were asked if they had taken folic acid during the last few months, what dose, as a single preparation or as a multivitamin and the exact period they used it. They were asked about their preference for supplementation or fortification, folic acid use during former pregnancies, and some demographic factors like age, education and ethnicity.

Frequent phone calls were made to the participating practices during the time of the survey to monitor the progress of the investigation and to improve the response. Only a few women refused to fill out the questionnaire. A total of 550 questionnaires were sent out and 515 were returned completed (response rate 94%). Not all respondents did answer every question, so the sum of all numbers in the tables may be less than 515.

The highest level of education of the respondent was taken as a proxy for their socioeconomic status. The seven levels of education, ranging from elementary school to university, were allocated to low, middle and high. Data were analyzed using SPSS 16. We used logistic regression analysis to investigate the interdependence of the most important factors that influence the use of folic acid by multivariate odds ratios. For this, women who started folic acid supplementation before conception were compared to women who did not use folic acid during the recommended period.

Results

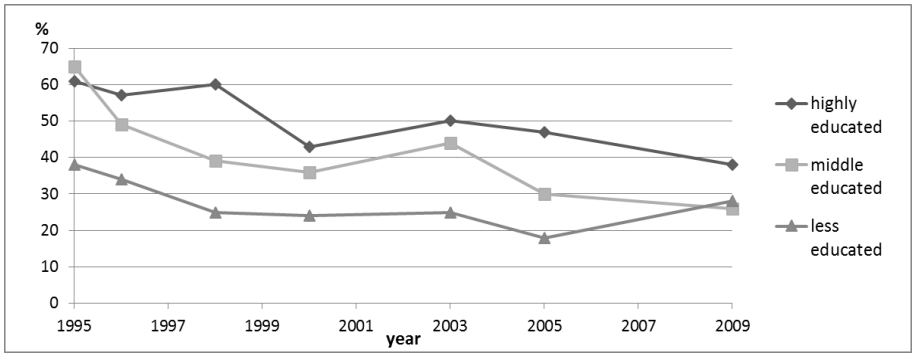
Knowledge

Of all women who participated in our study, 3.5% stated they had not heard about folic acid. 9.5% heard about folic acid when they were already pregnant. The other 87.0% heard about folic acid before they got pregnant. Among women who heard about folic acid, 76.1% knew that the use of folic acid is recommended to reduce the chance on spina bifida / NTD's and 32.2% could tell the actual period in which folic acid use is recommended.

Of all the women that had heard about folic acid 89.9% knew that women should start with folic acid before pregnancy and of the women who knew when to start, 71.1% actually did start to use folic acid before conception. Of all women knowing the recommended period for folic acid supplementation, 60.8% also used folic acid this entire period.

Figure 1 shows that the percentage of women knowing the recommended period of taking folic acid has not been improved since the start of the surveys in 1995.

Figure 1: Percentage of women knowing the recommended period of taking folic acid, by level of education.



Use

Of all respondents, 71 (14.6%) stated that they had not taken any folic acid during the recommended period at all, and 251 (51.6%) reported to have used folic acid during the entire recommended period. Of all participating women 312 (65.1%) started to take folic acid before pregnancy, and 415 (85.4%) used folic acid in any part of the recommended period. Of women that had heard about folic acid before pregnancy, 59.1% actually did use folic acid the entire recommended period.

Nearly 40% of all women who used folic acid any time during their pregnancy started with a multivitamin, and 8.5% changed from folic acid to a multivitamin containing folic acid during their use. At the time they completed the questionnaire, 76.4% of all these women still used a multivitamin. Of all women who only used folic acid, 52.8% still used it at the time they completed the questionnaire.

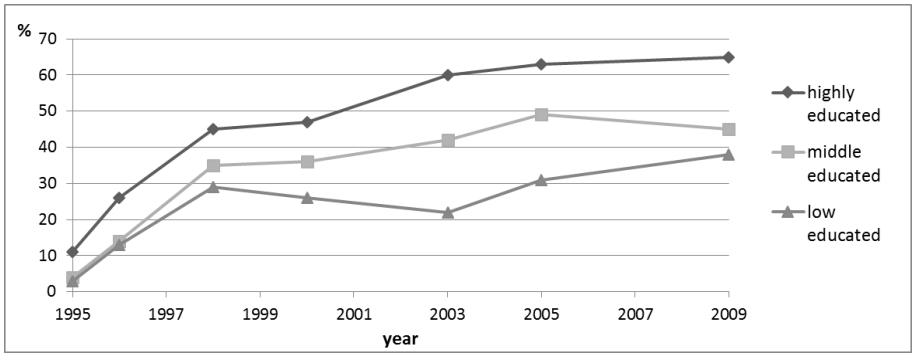
Table 1: folic acid use in 2005 and 2009.

	2005 n(%)	2009 n(%)	p-value
use			
no folic acid	87 (20.0)	71 (14.6)	0.030
folic acid use during part of the recommended period	126 (29.0)	164 (33.7)	0.119
folic acid use during the entire recommended period	222 (51.0)	251 (51.6)	0.853
total			0.062
knowledge			
heard about folic acid before pregnancy	397 (88.6)	448 (87.0)	0.443
heard about folic acid during pregnancy	28 (6.2)	49 (9.5)	0.263
not heard about folic acid	23 (5.1)	18 (3.5)	0.074
total			0.092
know about protective effect against NTD's	328 (77.2)	378 (76.1)	0.689
do not know about protective effect	97 (22.8)	119 (23.9)	
know recommended period	143 (33.6)	160 (32.2)	0.639
do not know recommended period	282 (66.4)	337 (67.8)	

As shown in Table 1, there has not been a significant change in folic acid use during the entire recommended period compared to the survey of 2005. Significantly less women reported no use of folic acid supplements at all during pregnancy (20.0 % in 2005 compared to 14.6% in 2009, p=0.03). Figure 2 shows the percentage of women using folic acid during the recommended period, by level of education, in time.

In this study 57.0% of women pointed out they preferred to keep taking folic acid as supplementation. Only 7% would prefer fortification. The other women did not prefer one of both options.

Figure 2: Percentage of women using folic acid during the recommended period, by level of education.



Factors that influence the use of folic acid

Table 2 shows the variables that were associated with folic acid use. The variables significantly associated with folic acid use were: planning of pregnancy, knowledge of folic acid (why it should be taken and which period), age of the respondent, level of education (as a proxy for socioeconomic status), smoking, parent with a non-western origin and the use of folic acid during a previous pregnancy, as well as already having children.

Multivariate analysis showed that women who smoke (OR 0.2 95% CI 0.1-0.7), and women with more children (OR per child: 0.5 95% CI 0.3-0.9) are less likely to use folic acid as recommended, while women who plan their pregnancy (OR 7.1 95% CI 2.4-20.7) and women who used folic acid during a former pregnancy (OR 22.6 95% CI 5.5-92.8) are more likely to use folic acid as recommended.

Sources of information

In the questionnaire women were asked about their sources of information about folic acid. Among women that had heard about folic acid, 76.6% mentioned the media as a source. These include papers, magazines, the Internet, books and television. Professional sources, like general practitioner, midwife, gynecologist and pharmacy were mentioned by 49.1% of these women. Since 1995 pharmacies add a sticker on every box of oral contraception with the text: "Are you planning to have a baby? Ask for information about folic acid in your pharmacy." This sticker was mentioned by 9.9% of women as a source of information. Family, friends and partner were mentioned by 36.4% as a source of information about folic acid.

Table 2: Factors influencing the use of folic acid during the recommended period.

	no use of folic acid (n-tot=71) n(%)	folic acid use in part of recom-mended period (n-tot=164) n(%)	folic acid use in entire recom-mended period (n-tot=251) n(%)	p-value
knowledge:				
heard about folic acid				
not heard about	18 (25.4)	0	0	
during pregnancy	16 (22.5)	27 (16,5)	0	
before pregnancy	37 (52.1)	137 (83,5)	251 (100)	<0.001
knowledge about the use of folic acid				
wrong answer	39 (54.9)	27 (16.5)	31 (12.4)	
prevetion NTD's	31 (43.7)	118 (72.0)	196 (78.1)	
congenital abn. / central nervous system (CNS)	1 (1.4)	19 (11.6)	24 (9.6)	<0.001
knowledge about period				
wrong period	55 (77.5)	120 (73.2)	158 (62.9)	
right period	16 (22.5)	44 (26.8)	93 (37.1)	0.019
behaviour:				
planned pregnancy				
no	36 (50.7)	61 (37.2)	22 (8.8)	
yes	35 (49.3	103 (62.8)	229 (91.2)	<0.001
use of contraception before pregnancy				
none	20 (28.2)	35 (21.3)	49 (19.5)	
oral contraceptives	32 (45.1)	74 (45.1)	133 (53.0)	
other	19 (26.8)	55 (33.5)	69 (27.5)	0.298
use of folic acid during a former pregnancy				
no	18 (25.4)	11 (6.7)	3 (1.2)	
yes	25 (35.2)	89 (54.3)	147 (58.6)	<0.001
sources:				
mediasources				
no	13 (18.3)	37 (22.6)	50 (19.9)	
yes	40 (56.3)	127 (77.4)	201 (80.1)	0.681
paper/magazine	18 (25.4)	77 (47.0)	116 (46.2)	0.222
books	9 (12.7)	54 (32.9)	96 (38.2)	0.011
Internet	22 (31.0)	77 (47.0)	128 (51.0)	0.402
tv / radio	0 (0)	6 (3.7)	24 (9.6)	0.007

Table 2 – continuation.

	no use of folic acid (n-tot=71) n(%)	folic acid use in part of recom-mended period (n-tot=164) n(%)	folic acid use in entire recom-mended period (n-tot=251) n(%)	p-value
proffesional sources				
no	32 (45.1)	66 (40.2)	131 (52.2)	
yes	21 (29.6)	98 (59.8)	120 (47.8)	0.012
general practicioner	9 (12.7)	40 (24.4)	38 (15.1)	0.058
midwife	8 (11.3)	44 (26.8)	45 (17.9)	0.051
gynecologist	6 (8.5)	14 (8.5)	19 (7.6)	0.664
pharmacist	3 (4.2)	5 (3.0)	12 (4.8)	0.604
folder in pharmacy	0 (0)	9 (5.5)	20 (8.0)	0.082
sticker on oc	2 (2.8)	16 (9.8)	30 (12.5)	0.197
others				
no	28 (39.4)	111 (67.7)	156 (62.2)	
family / friends	25 (35.2)	53 (32.3)	95 (37.8)	0.137
Lifestyle:				
alcohol				
no	46 (64.8)	91 (55.5)	133 (53.0)	
stopped	2 (2.8)	6 (3.7)	19 (7.6)	
went to drink less	3 (4.2)	11 (6.7)	29 (11.6)	
yes	20 (28.2)	56 (34.1)	70 (27.9)	0.080
smoking				
no	37 (52.1)	108 (65.9)	203 (80.9)	
stopped	2(2.8)	6 (3.7)	9 (3.6)	
went to smoke less	6 (8.5)	11 (6.7)	9 (3.6)	
yes	26 (36.6)	39 (23.8)	30 (12.0)	p<0.001
demographic factors:				
age				
<20	6 (8.5)	0	0	
20-24	16 (22.5)	31 (18.9)	17 (6.8)	
25-29	17 (23.9)	55 (33.5)	76 (30.3)	
30-34	19 (26.8)	56 (34.1)	102 (40.6)	
>34	13 (18.3)	20 (12.2)	56 (22.3)	<0.001
level of education				
low	21 (29.6)	27 (16.5)	29 (11.6)	
middle	34 (47.9)	82 (50.0)	95 (37.8)	
high	14 (19.7)	54 (32.9)	127 (50.6)	<0.001
parity				
no children yet	35 (49.3)	70 (42.7)	122 (48.6)	
one previous child	17 (23.9)	67 (40.9)	101 (40.2)	
more than one previous child	19 (26.8)	27 (16.5)	28 (11.2)	0.006
country of birth				
The Netherlands	63 (88.7)	151 (92.1)	235 (93.6)	
other Western country	2 (2.8)	3 (1.8)	8 (3.2)	
non-Western country	6 (8.5)	9 (5.5)	8 (3.2)	0.359
country of birth of one of the parents				
Western country or the Netherlands	62 (87.3)	146 (89.0)	239 (95.2)	
non-Western country	9 (12.7)	17 (10.4)	11 (4.4)	0.018

Discussion

Most Pregnant women know about folic acid, and 76.1% could mention that it prevents NTDs but only 32.2% knew about the recommended period of use. Compared to the first survey of 1995, which was performed two years after the start of the folic acid campaign, the results are even worse. An overall decline is seen in the knowledge about the recommended period, especially for higher and middle educated women. At the 2009 survey, one third of the women were able to mention the recommended period for the use of folic acid. Despite increased attention this is lower than in former years (Figure 1).

At the 2009 survey, 51% of the respondents took folic acid in the recommended period and this percentage has not increased since the survey of 2005. However, less women reported no use of folic acid supplements at all during pregnancy (20.0 % in 2005 compared to 14.8% in 2009, p=0.04).

Figure 2 shows a minor decrease of folic acid use during the recommended period among high and middle educated women and an increase among low educated women. Although there is no statistical significant difference in the amount of women taking folic acid during the recommended period between the surveys of 2005 and 2009 for the different levels of education (p=0.24, p=0.14 and p=0.87), the existing difference between high- and low-educated women has the tendency to reduce.

Of all respondents, three-quarter indicated their pregnancy to be planned. These are very high rates according to the rest of Europe [3,4]. Most women that only use folic acid during a part of the recommended period do not start early enough. So planning of pregnancy is very important for the right use of folic acid. Although a planned pregnancy is a good predictor of the recommended use of folic acid, still 37.6% of all women who planned their pregnancy did not use folic acid during the recommended period. Only 39.2% of women, who know the recommended period of use, actually followed this recommendation. Women should be more aware of the impact of NTD's and the importance of the protective effect of folic acid.

Maternal age and socioeconomic status are relevant factors for the use of folic acid by pregnant women. Women of low economic status and young age are less apt to plan their pregnancies and their knowledge about folic acid falls short. Therefore it is of great importance to reach young, less educated women with information about the recommended use of folic acid. Providing information about family planning and the use of contraceptives should also be a key point in reducing the amount of NTD's.

The sticker that pharmacies add on boxes with oral contraceptives is mentioned by 10 % of women as a source of information about folic acid. This proportion has significantly decreased compared to the survey of 2005 (14.6%, p=0.02).

The participating pharmacies should be asked whether the sticker has been added on the boxes consistently. To catch the eye, the sticker might be given a color that is more intense and a text that is more explicit.

Only 50.9% of women mention professionals as source of information about folic acid. They often get in touch with a health care professional for their pregnancy when they are already pregnant. Women in childbearing age should get information about folic acid from their general practitioner or pharmacist, whenever they get in contact. Posters and flyers about folic acid should be available in general practices, hospitals and pharmacies and should be renewed every year, to keep attracting women in fertile age. Information about folic acid should be integrated in the government's policies regarding preconception care.

Besides the effect of folic acid on the occurrence of NTD's, several studies have documented positive effects on the occurrence of other congenital abnormalities, like congenital heart defects [10]. A preventive effect of folic acid on the occurrence of preterm birth has also been found by Czeizel et al when used until the end of pregnancy [11]. There is also still discussion whether the use of a multivitamin containing folic acid would be more effective than a supplement containing only folic acid [12].

Of all women using a multivitamin during their pregnancy, significantly more were still using it at the time they completed the questionnaire compared to women using only folic acid ($p<0.000$). Multivitamins are often used for general health of both mother and child during the entire pregnancy. Because the questionnaire was completed by women at different stages of their pregnancy, some might have switched or stopped later on. Advising women to start using a multivitamin containing at least 0.4 mg folic acid, 4 weeks before conception until delivery might have several advantages and more research on this topic needs to be done.

The decline in use of folic acid in pregnancy might be influenced by the discussion about the relation, although controversial, of folic acid and the development of cancer. Epidemiologic studies are inconsistent concerning a protective effect of folate intake on the risk of breast cancer [13]. Several studies suggest a beneficial effect on the development of new malignancies as well as a negative effect on the development of already existing or premalignant lesions [14-16].

Because of these concerns there is still a discussion in the Netherlands and the rest of Europe, whether to keep recommending women to use folic acid supplementation during their pregnancy, or to start with the fortification of certain kinds of food, as has been done in the US and Canada. The controversial outcomes might plead against the fortification of food with folic acid, especially because only 7% of the women in this study would prefer fortification. On the other hand, earlier research [1,2,17] showed that up to 80% of NTD's can be avoided by adequate intake of folic acid. The first recommendations about the perinatal intake of folic acid were introduced in Europe in 1993.

Several studies [18,19] showed hardly any changes in the prevalence of NTD's associated with these recommendations, indicating that mere recommendations are hardly effective in reducing the amount of NTD's.

In the Northern Netherlands folic acid use during the recommended period increased from less than 10% in 1995 to 51% in 2005 and it did not change since. Busby et al found a significant decline in the prevalence of NTD's in the Northern Netherlands of 43% when they looked at the period between 1989 until 2002, where they found a total prevalence rate of 6.5 per 10.000 births in the period 2000 - 2002. In their study [18], Khosnood et al found a total prevalence rate of NTD's of approximately 7 per 10.000 in the period 2004 - 2008, indicating that since the use of folic acid during the recommended period stopped increasing, the NTD rates leveled as well [20].

Our study had certain limitations. A lot of women who completed the questionnaire could not tell the dose of folic acid they had been taking. If a woman had used a tablet containing only folic acid, it was scored within the group of 0.4/0.5 mg, because most over the counter tablets contain one of these doses. When a woman had taken a multivitamin, the brand was often unknown, making it hard to obtain the amount of folic acid they had actually taken. Only a few women of non-western origin participated in the survey, and the overall numbers were too small to draw conclusions about this group of non-western immigrants. 39.5% of all women indicated to be high-educated. This might be an overestimation because high-educated women tend to fill in a questionnaire sooner than low-educated women. The average number of high-educated women in the northern Netherlands is about 20%, including women of 45 to 65 years of age, who are more often low-educated. A recent Dutch study by Lanting et al about smoking during pregnancy found 37.5% of women to be high-educated, which is close to the percentage we found [21].

In conclusion

It is time for new initiatives to increase knowledge about the use of folic acid among women who plan to get pregnant. These initiatives should focus on younger, low-educated women and should include information about family planning and contraception. Information about folic acid should be given by physicians and pharmacists to any woman in childbearing age, and it should be integrated in preconception care. Given the fact that only half of all pregnant women are taking folic acid as recommended and the NTD rates leveled as well in the last couple of years, there is still a lot to gain in the prevention of NTD's.

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Chapter 2.2 Folic acid use around pregnancy in the Netherlands, still sustainable after 20 years?

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Abstract

Background

The awareness and the actual use of folic acid by pregnant women has been monitored periodically in the Northern Netherlands since 1995. To investigate the sustainability of folic acid use around pregnancy, a subsequent survey was carried out in 2014.

Methods

573 surveys were distributed to pregnant women attending their prenatal visits at regional obstetric practices and gynaecologic departments. 285 completed questionnaires were returned, leading to a response rate of 49.7%.

Results

In total, 267 women entered information to enable determination of the period of folic acid use of whom 64.8% (n=173) started with folic acid supplementation before conception. Recommended folic acid use from 4 weeks before conception until 8 weeks thereafter could be determined for 56.2% (n=150).

Conclusion

Folic acid supplementation around pregnancy to prevent the development of a neural tube defect has stabilized during the last decade.

Background

Since the early nineties, The protective effect of folic acid supplementation on the development of neural tube defects is without a doubt and risk reduction of other birth defects has also been suggested [1-3]. Furthermore there have been indications that folic acid may prevent other negative infant and maternal outcomes, like preeclampsia, preterm birth and some forms of paediatric cancer [4]. Therefore the World Health Organization (WHO) recommends that: "All women, from the moment they begin trying to conceive until 12 weeks of gestation, should take a folic acid supplement (400 µg folic acid daily)" [5].

Guidelines about periconceptional folic acid use were implemented in the Netherlands in the nineties of the twentieth century and ever since several interventions were unrolled to promote the use of folic acid before and during pregnancy. From the start of the implementation 20 years ago, the awareness and the actual use of folic acid by pregnant women has been monitored periodically [6]. The latest study from 2009 shows that proper use of folic acid seems to level off at a little over 50% [6].

To investigate the sustainability of folic acid use around pregnancy, a subsequent survey was carried out in 2014 in the Netherlands.

Methods

To ensure continuity the 2014 survey was carried out in the same area in the Northern Netherlands as the previous surveys were. We distributed 573 questionnaires to 8 obstetric practices and gynaecologic departments that agreed to have the questionnaires completed by the pregnant women attending their prenatal visits. Participants were asked to provide information about some maternal characteristics, certain life style factors like smoking and alcohol use, their knowledge about folic acid and details about their use of folic acid supplements.

With previous surveys, the midwiferies and gynaecology departments handing out the surveys were given an incentive for every completed survey returned. For the 2014 survey no money was available for incentives, yet only one midwifery declined participation because of their involvement in other studies.

Participating practices were contacted several times during the study period to ask about the progress. One midwifery indicated that they were not able to carry out the survey after all because of a number of other investigations running. Finally, 285 completed questionnaires were returned out of the 573 distributed, leading to a response rate of 49.7%.

Information about gestational length and start and stop dates of folic acid use were used to calculate the pregnancy period in which folic acid supplementation was taken. Recommended folic acid use was defined as the intake of a supplement containing at least 0.4mg folic acid from at least 4 weeks before conception until 8 weeks thereafter, according to Dutch guidelines [7]. Use of folic acid in 2014 was compared to use in 2009 and surveys before.

Results

The study sample of the 2014 survey was comparable to the sample recruited in 2009 in respect to maternal age, onset and planning of pregnancy, and smoking and alcohol use during current pregnancy (Table 1). The current 2014 survey recruited less low-educated women and women with a first pregnancy. In 2014, participating women completed the questionnaire on average later in pregnancy than the women in 2009.

Table 1: Comparison of maternal characteristics in the 2009 and 2014 survey

	2009		2014		p-value
	n-tot	n (%)	n-tot	n (%)	
age (mean, sd)	513	29.9 (5.1)	277	29.6 (4.7)	0.373
educational level – low (n (%))	506	83 (16.4)	268	26 (9.2)	**0.011**
educational level – middle (n (%))	506	221 (43.7)	268	122 (45.5)	0.623
educational level – high (n (%))	506	202 (39.9)	268	120 (44.8)	0.192
gestational duration (mean, sd)	506	19.8 (12.5)	265	25.8 (9.9)	**<0.001**
parity – nullipara (n (%))	514	203 (39.5)	285	92 (32.3)	**0.043**
onset of pregnancy – spontaneously (n(%)	515	484 (94.0)	285	266 (93.3)	0.717
planned pregnancy (n (%))	515	389 (75.5)	285	215 (75.4)	0.976
smoking during current pregnancy – yes	515	149 (28.2)	285	70 (24.6)	0.184
alcohol during pregnancy – yes	515	222 (43.1)	285	141 (49.5)	0.083

Folic acid use according to guidelines is related to educational level. Figure 1 shows the course over time of folic acid use as recommended in percentages, divided by educational level. The gap in recommended folic acid use between high educated and low/middle educated women is still apparent (p=0.001) and it has even increased. Multivariate logistic regression analysis showed that this relation is mainly caused by younger maternal age and less planning of pregnancy for lower educated women as predictive factors for recommended folic acid use. Figure 2 shows the relation between planning of pregnancy and maternal age with educational level.

Figure 1: Course of correct folic acid use in percentages, by educational level.

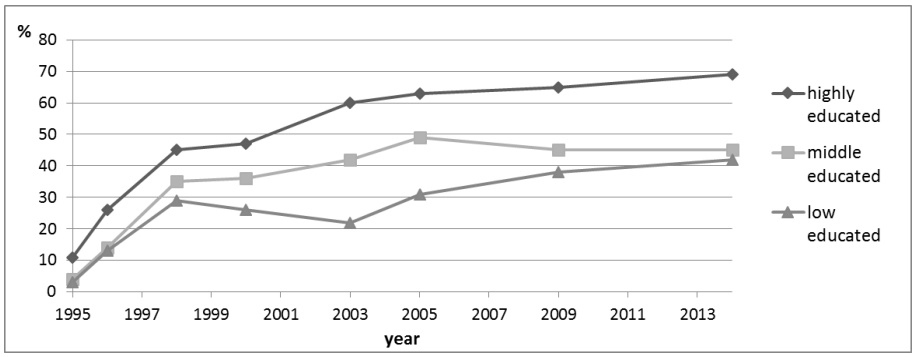
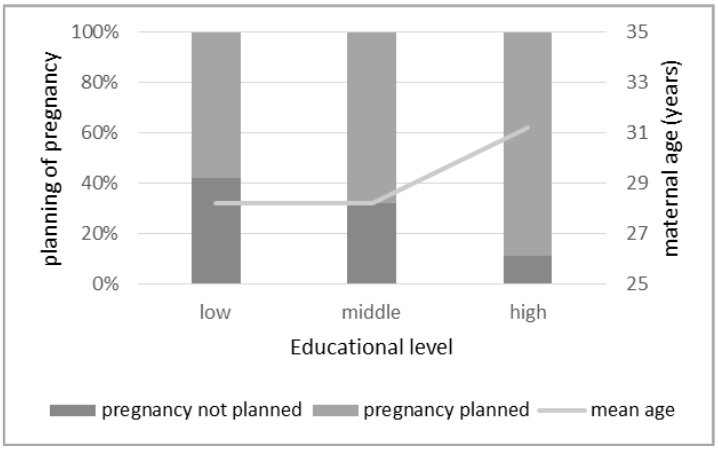


Figure 2: Planning of pregnancy and mean maternal age by educational level.



Most of the women completing the 2014 survey had heard about folic acid before they were pregnant (250 out of 253, 88.3%). 9.9% (n=28) was already pregnant when they learned about folic acid and only 1.8% (n=5) had not heard about folic acid up to that point. The main source of information about folic acid was the Internet, mentioned by 139 women (48.8%), followed by the midwife, mentioned by 39.6% of women (n=113).

Discussion

Recommended use of a folic acid supplement before and during pregnancy has not significantly changed during the last decade. Despite the absence of new media campaigns, folic acid use according to guidelines maintained at a level of just over 50%. Almost two third of women started with folic acid supplementation before conception. These numbers are much better than figures from the rest of Europe.

A special report from the European surveillance of congenital anomalies (Eurocat) about the prevention of neural tube defects by periconceptional folic acid supplementation in Europe shows percentages for recommended folic acid use around pregnancy from 2005 - 2007 for cases included in their registry of less than 10% for most regions involved, except for the Northern Netherlands and Odense (Denmark) with percentages of approximately 40% and 30% respectively [8]. A recent study however only found 10.4% recommended folic acid use in pregnant women attending for a routine scan in a Copenhagen hospital, even though 82% of pregnancies were planned [9].

Folic acid use in our surveys might actually be a little overestimation. Next to the lower estimate in the Eurocat report, Mannien et al analysed folic acid use in a Dutch population-based pregnancy cohort and reported folic acid supplementation started before conception to be 55.5% [10]. These scores sound low, but levels of 100% can never be reached. There will always be unplanned pregnancies and uninformed, indifferent or non-convinced women, in spite of good information.

Almost 90% of participating women knew about folic acid before they got pregnant. On the Internet, there are thousands of pages discussing pregnancy and the benefits of folic acid use. But although most pregnant women in developed countries have access to the Internet and use it to search for pregnancy-related information before and in the beginning of their pregnancy [11,12], not even half of the participating women mentioned Internet as a source of information about folic acid. Women might not remember to have read information about folic acid on the Internet due to the load of information they got and they might have heard about folic acid via other sources first.

The second most mentioned source, the midwife, is often only visited for the first time when the recommended period for folic acid supplementation has already passed and therefore he/she has a minor role in the promotion of starting folic acid supplementation in time. On the other hand, they can have a substantial contribution by emphasizing the importance of a timely start on the webpage of their practice.

The absence of an incentive for the participating practices for every completed questionnaire returned and the involvement in other studies affected the response rate of the 2014 survey. With earlier surveys the questionnaires were all handed out to the pregnant women at one of their first visits and they were personally asked to complete and return the form, leading to response rates of 75-94% [6,13].

With the latest survey, some of the practices placed the questionnaires in their waiting room and some of the co-operating health care workers indicated that they did not want to overcharge women with all the studies running. Remarkably, a substantial part of the questionnaires got lost at the participating practices. The lower response rate of the latest survey might have led to selection bias, but the similarities of the 2009 and 2014 sample regarding maternal age and planning of pregnancy suggests little effect on folic acid use estimates. The strategy changes resulted in a sample that was recruited later in pregnancy than in earlier surveys, which might have led to lower remembrance of start and stop dates of folic acid supplementation and higher use of multivitamins, which are often started later in pregnancy.

In Conclusion:

Folic acid supplementation around pregnancy to prevent the development of a neural tube defect has stabilized during the last decade. Although 82% of pregnancies in our sample were planned, only 56% of women used a folic acid supplement in accordance with Dutch guidelines. Since health care providers are often only contacted after identification of a pregnancy at present, reimbursed pre-pregnancy counselling offered to everyone planning a pregnancy might increase recommended folic acid supplementation considerably.

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Chapter 2.3 Evaluation of the representativeness of a Dutch non-malformed control group for the general pregnant population: are these controls useful for EUROCAT?

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Abstract

Purpose

A case–control study is the most powerful design to test the risk of specific congenital malformations associated with a specific drug. However, malformation registries often lack non-malformed controls. For the Dutch EUROCAT, we collected a non-malformed control group: the 'Healthy Pregnant'. The aim of this study was to evaluate the representativeness of this control group for the general pregnant population in the northern part of the Netherlands.

Methods

The Healthy Pregnant data set includes data from two midwife practices. The baseline characteristics of mother and child including smoking status, drinking status, body mass index, maternal age, educational level, exposures to several drugs for chronic diseases and pregnancy related symptoms were evaluated.

Results

Compared with the general population, mothers in the Healthy Pregnant group (n=556) were from either low or high education level, were more likely to have a body mass index >25 kg/m2 (26% versus 22%, p=0.08) or to smoke (19% versus 10%, p<0.01) but were less likely to consume alcohol (20% versus 29%, p <0.01). The use of drugs for chronic conditions was lower in the Healthy Pregnant group. Furthermore, drugs for occasional use were prescribed less frequently, and a significant underreporting of children with a low birth weight and a short duration of gestation was found.

Conclusion

The Healthy Pregnant data set was not representative for the general pregnant population in the northern part of the Netherlands. Specifically, the exposure to (chronic) drugs was underestimated, possibly a result of second-line care on the basis of medical indication. Thus, continuous investigation of options for improvement of the Healthy Pregnant database is required.

Introduction

Case–control studies that were designed to test the teratogenicity of drugs using chromosomal or other malformed controls are often criticised for the validity of the control group [1,2]. In particular, these control groups were generally derived from the same data sources and were collected and validated using the same methods as those for the malformed cases. One advantage of such an approach is that malformed controls might give the opportunity to (partially) correct for potential recall bias because both mothers could feel 'guilty' and therefore tend to remember more about drug exposure, especially drugs used for a short period [3-5]. However, the debate remains because it cannot be assured that there is no association between the malformations in a 'malformed control group' and the drug under study. If there is an association, it would cause an underestimation of the effect size [2].

Because registries of congenital malformations often lack information about non-malformed subjects, the use of an external non-malformed control group could be an appropriate alternative. Ideally, the non-malformed control group and malformed cases would originate from the same population. However, there are also limitations associated using external control groups. These include data collection methods that are (slightly) different, study populations that are not (exactly) the same (smaller region, different years), less detailed data or registered controls that are only composed of a population sample. Furthermore, the collection of data on population-based control groups that cover the same total population as the malformed group is generally labour intensive and therefore costly.

To address criticisms in the literature, we collected data for a non-malformed control group for use in case–control studies with the Dutch EUROCAT, a data set including pregnancy outcomes with congenital malformations. The aim of this study was to evaluate representativeness of a non-malformed control group from the northern part of the Netherlands to the general Dutch pregnant population.

Methods

EUROCAT

EUROCAT is a European network of population-based pregnancy outcome registries collecting data on malformations for epidemiologic surveillance purposes. Since 1981, the Dutch EUROCAT registry has collected data on major congenital malformations in the northern part of the Netherlands.

After the birth of an infant diagnosed with a malformation or termination of pregnancy after prenatal diagnosis of a malformation, parents were asked to give consent for registration in the EUROCAT database. A written questionnaire was filled out by the parents, and the pharmacy history of the mother was collected. Answers to the questionnaire and data on drug use were verified in a phone interview with the mother. Hospital data were used mainly for the classification of the malformation (*International Classification of Diseases* code). Because both pregnancy outcome and drug exposure history were well registered, the data were considered suitable for use in a case–control monitoring system. However, detailed population-based data were available only for major congenital malformed pregnancy outcomes and not for non-malformed pregnancy outcomes.

'Healthy Pregnant'

The 'Healthy Pregnant' (*Gezond Zwanger* in Dutch) database was started in 2004. Starting with a midwifery practice in a rural small city, Veendam (28000 inhabitants), the programme was later extended to include a midwifery practice located in the university hospital of Groningen in 2008. Data collection procedures were consistent with the EUROCAT way of working. Pregnant women were asked by the midwife for consent at the beginning of their pregnancy (during their first or second consult). Women were included via the midwife practices because all women were expected to start prenatal care in a primary care setting. After birth, the verification of any malformations was conducted by the midwife. If there was no diagnosis of malformations, the parents were asked to fill out a written questionnaire and the pharmacy history of the mother in addition to a list of symptoms and possible use of over-the-counter drugs was sent to the mother for confirmation. The questionnaires for both Healthy Pregnant and EUROCAT databases were similar, resulting in the collection of the same information for both data sets. Initially, the collected data were verified by a phone interview comparable with the interview used in EUROCAT registry procedure. However, because hardly any new information was obtained with these time-consuming interviews, verification by phone was discontinued in June 2007.

Baseline characteristics

To compare the Healthy Pregnant with the general pregnant population, we evaluated the following baseline characteristics: gender of the child, age of the mother, body mass index (BMI; weight in kg/m^2) of the mother before pregnancy, smoking status and alcohol consumption during pregnancy, educational level of the mother, folic acid use of the mother and use of any specific medication. The classification of drugs was based on the Anatomical Therapeutic Chemical (ATC) code, which is comparable with the classification used in an earlier study using the IADB.nl database [6].

The IADB.nl is a pharmacy prescription database covering the prescriptions of about half million people located in the same area as the EUROCAT registry. In this study, we focused on four types of chronic therapies, that is, antidiabetics (A10), antiepileptics (N03), antipsychotics or antidepressants (N05A excl. N05AB04, N06a) and antiasthmatics (R03), and some short-term or pregnancy-related therapies, that is, antacids (A02A), antiemetics (A03FA01, A04A, N05AB04, R06AD and R06AE), iron preparations (B03A), gynecological anti-infectives and antiseptics (G01), ovulation stimulants (G03G) and antibiotics (J01).

The baseline characteristics listed in the previous paragraph were gathered from several sources. The pregnancy database of the IADB.nl, which covers the pharmacy data of pregnancies in the same area as EUROCAT, was used to compare the age of the mother and the use of drugs during pregnancy [7]. All pregnancies with a delivery between 1 January 2004 and 31 July 2009 were selected from the IADB.nl database. In total, 5517 pregnancies were covered by the IADB.nl in this period. Data from the Central Bureau of Statistics (Dutch Statistics) based on Dutch women aged 25 to 35 years were used as a comparator for the BMI of mothers included in the study [8]. The results of a folic acid monitoring study in the northern part of the Netherlands—including 515 pregnant women in 2009—were used to compare folic acid use [9]. A survey of approximately 14 500 pregnant women in the Netherlands (not specific from the northern part) in 2001 to 2007 was used to compare the smoking status, the alcohol consumption and the educational level of the mother [10]. Furthermore, data of more than 70 000 births reported in the Perinatal Registry Netherlands in 2004 to 2007 were used for the comparison of gender, duration of gestation and birth weight of the child [11]. The Perinatal Registry Netherlands data set included almost all births in the Netherlands.

Analyses and statistics

Statistical analysis was conducted using the Statistical Package for the Social Sciences (version 16.0; SPSS Inc., Chicago, IL), R.2.10.1 and Excel 2003 by performing chi-square tests with Yate's correction or *t*-tests and by calculating confidence intervals.

Results

Five-hundred and fifty-six children who were born between 16 December 2004 and 30 July 2009 were registered in the Healthy Pregnant database.

Table 1: Descriptive frequencies of the characteristics of mother and child for 'Healthy Pregnant' and the reference groups.

	'Healthy pregnancy'*	Reference*	p-value
sex of the child	n=531	n=710,282†	
male (%)	49.7%	51.3%	0.701
duration of gestation	n=556	n=703,839†	
< 32 weeks (%)	0.5%	1.6%	0.073
< 37 weeks (%)	4.1%	7.9%	**0.003**
≥ 41 weeks (%)	24.8%	22.6%	0.294
birth weight	n=527	n=688,756†	
< 2000 gram (%)	1.1%	3.0%	**0.019**
< 2500 gram (%)	3.2%	7.1%	**0.001**
≥ 4000 gram (%)	18.2%	16.0%	0.262
≥ 4500 gram (%)	3.6%	2.9%	0.398
mean age at birth	n=556	n=5,517‡	
1st child (years, standard deviation)	28.7 (4.2)	29.1 (5.1)	0.463
all children together (years, standard deviation)	29.9 (4.4)	30.0 (4.8)	0.694
body mass index (BMI) mother	n=515	n=NA$	
underweighted BMI <18.5 (%)	2.1%	3.2%	0.237
intermediate BMI 18.5-25 (%)	58.3%	65.9%	0.105
over weighted or obese BMI ≥ 25 (%)	26.2%	21.9%	0.079
obese, BMI ≥ 30 (%)	13.4%	9.0%	**0.003**
smoking during pregnancy	n=528	n=14553**	
yes (%)	18.9%	9.7%	**<0.001**
alcohol consumption during pregnancy	n=529	n=1839**	
yes (%)	20.2%	28.6%	**0.004**
folic acid	n=486	n=509 ††	
correct (min. 4wks<conception>8wks) (%)	46.4%	51.6%	0.358
some (%)	42.2%	33.7%	0.074
no (%)	11.4%	14.6%	0.219
educational level	n=508	n=13944**	
lower vocational training (%)	48.4%	22.4%	**<0.001**
intermediate vocational training (%)	9.4%	40.1%	**<0.001**
higher vocational training/university (%)	42.1%	37.5%	**<0.001**
medication for chronic use in the 1st trimester‡‡	n=556	n=5517‡	
antidiabetics	0	5.4	0.156
antiepileptics	0	2.5	0.470
antipsychotics and antidepressants	5.4	27.6	**0.003**
antiasthmatics	36.0	30.8	0.606
medication use of other drug in pregnancy‡‡	n=556	n=5517‡	
antacids	54.0	120.2.	**<0.001**
antiemetics	54.0	91.7	**0.007**
iron preparations	30.6	236.2	**<0.001**
gynecological anti-invectives and antiseptics	152.9	188.3	0.096
ovulation stimulants	14.4	21.0	0.380
antibiotics	178.1	213.3	0.124

* n= total number available for analysis for this characteristic. Not all variables include all women as not all information was available for each of them.
Reference group used: † Perinatal Registry Netherlands, ‡ IADB.nl, $ CBS, ** Survey, Lanting et al, †† Folic acid monitor [7-11].
‡‡ for all subgroups presented as prevalences per 1000 pregnancies

Eighty-five percent of all registered pregnancies were taken care of by the midwifery practice in Veendam, and the other 15% was derived from the midwifery practice in Groningen. The descriptive frequencies of the characteristics of mother and child for both the Healthy Pregnant and the reference group are presented in Table 1. For both groups, the age of the mothers and the gender distributions of the newborns were similar. However, the Healthy Pregnant mothers were more often obese, tended to smoke more and reported less alcohol consumption and the educational level was either high or low. In the Netherlands, approximately 40% of all women in the fertile age finished an intermediate vocational training. However, in our data set, less than 10% had an intermediate training as the highest completed education.

After stratification on educational level (comparing low or intermediate, with high), it was found that a lower educational level is associated with significant higher smoking status (26% versus 11%), less alcohol consumption (12% versus 34%), higher risk for a BMI ≥25 kg/m^2 (47% versus 28%), less frequent use of folic acid during the advised period of at least 4 weeks before conception until 8 weeks into pregnancy (40% versus 55%) and younger age of the mother at birth of the child (Table 2).

Table 2: Smoking, alcohol consumption, body mass index (BMI), folic acid use and maternal age stratified by educational level among women in 'Healthy Pregnant'.

	Low or intermediate educated women	High educated women	p-value
smoking - yes	26%	11%	**<0.001**
alcohol - yes	12%	34%	**<0.001**
BMI >25	47%	28%	**<0.005**
folic acid use - correct	40%	55%	0.063
mother's age <25 yr	14%	4%	**<0.001**
mother's age <30 yr	53%	38%	**0.004**

A lower educational level is also associated with a lower socioeconomic status, which is known to increase the prevalence of smoking. Since we did find an increased prevalence of smokers, we stratified our data according smoking status during pregnancy to investigate if the proportion of smokers was different from the general population for different education levels (Table 3). We found significantly more higher-educated women who smoked during pregnancy in the Healthy Pregnant group compared with the general population (23% versus 14%). We also observed that non-smokers reported more alcohol consumption (19% versus 9%). However, we did not find associations between smoking and alcohol consumption or duration of gestation and smoking status.

Table 3: Educational level, alcohol consumption and gestational duration, stratified by smoking status among women in 'Healthy Pregnant' compared with the general population.

	Smokers			Non-smokers		
	'Healthy Pregnant'	refe-rence	p-value	'Healthy Pregnant'	refe-rence	p-value
educational level - low/intermediate	77%	86%	0.520	53%	60%	0.172
educational level - high	23%	14%	0.050	47%	40%	0.087
alcohol consumption - yes	26%	18%	0.273	19%	9%	<0.001
alcohol consumption - no	75%	82%	0.658	81%	91%	<0.001
duration of gestation <32 wks	1%	2%	0.764	0%	1%	0.980
duration of gestation <37 wks	3%	7%	0.210	4%	5%	0.489
duration of gestation ≥37 wks	96%	91%	0.776	96%	94%	0.901

Figure 1: Prevalence of first trimester exposure to drugs used for chronic indications among women in 'Healthy Pregnant' compared with the general population.

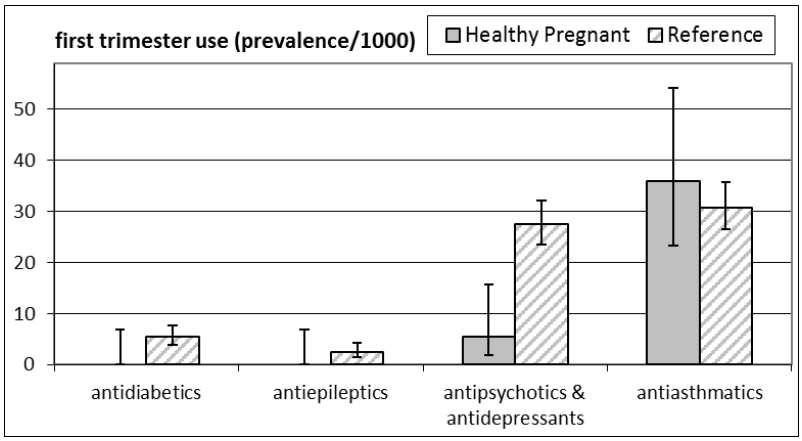
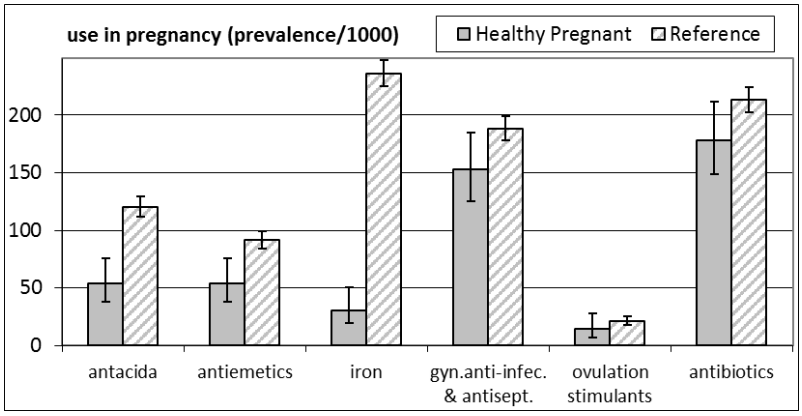


Figure 2: Prevalence of exposure to drugs used for occasional symptoms during pregnancy among women in 'Healthy Pregnant' compared with the general population.



Except for anti-asthmatics, the exposure to drugs for chronic indications during the first trimester of pregnancy (and also during the entire pregnancy) was lower among women in Healthy Pregnant compared with the general pregnant population (Figure 1). None of the women were exposed to antiepileptics or antidiabetics, and we did not identify women with pregnancy diabetics. The exposure to antipsychotics or antidepressants was significantly lower for the Healthy Pregnant compared with the general population with 5.4 per 1000 versus 27.6 per 1000, respectively. Several commonly used drugs for occasional symptoms were less often prescribed to women in Healthy Pregnant (Figure 2). In particular, the most significant difference was found for iron preparations (3% versus 24%), but antacids, antiemetics and gynecological anti-infectives and antiseptics were also prescribed less often in the Healthy Pregnant women.

Discussion

The Healthy Pregnant database is not representative for the general pregnant population in the northern part of the Netherlands. In particular, we found higher BMI, more smokers, less alcohol consumption and differences in educational level. Moreover, the exposure to (chronic) drugs is underrepresented, which could be due to direct referral to the gynaecologist on the basis of medical indication.

In Healthy Pregnant database, we only included information of pregnancies taken care of by the midwife. High-risk pregnancies were cared for by gynaecologists and were therefore missing in our data set. However, women who were referred to the gynaecologist after a consult with the midwife were included because the midwife provided the checks after birth. According to the current data, having a chronic disease like diabetes, epilepsy, depression or psychotic diseases is considered to be enough reason to start with second-line care. On the other hand, the use of anti-asthmatic or ovulation-stimulating drugs does not always result in direct second-line care. For these drugs, prevalence of use was comparable between the two groups.

We also observed an underrepresentation of low birth weight and duration of gestation. Both factors are associated with high-risk pregnancies and, consequently, are more likely to be cared for by a gynaecologist. In the Healthy Pregnant group, it was found that women from both low and high education levels were overrepresented whereas women of intermediate education were underrepresented.

Educational level is often used as a proxy for the socioeconomic status. From the literature, it is generally known that women with a lower socioeconomic status smoke more, consume less alcohol (but if they do, the amount consumed is generally larger), are more frequently overweight (or even obese), are less likely to use folic acid during the entire advised period and have children at a younger age [12-15]. When the analyses were stratified for educational level, the results confirmed the abovementioned trends (Table 2). The percentage of women who smoke during pregnancy in the Healthy Pregnant group is twice that of the reference group (Table 1). After stratification on smoking status, it was found that for the lower educated women, smoking status was similar between the two groups. However, for women with higher education, smoking during pregnancy was observed more often in the Healthy Pregnant group, which was an unexpected result.

A limitation of our evaluation is the relative small sample of pregnancies included in the Healthy Pregnant group. For example, the use of drugs for chronic indications during pregnancy was generally not very prevalent. Therefore, our confidence limits were quite wide, and although we do not have any pregnancy with exposures to antiepileptics or antidiabetics, there was still no significant difference observed. We are not convinced that there is no underrepresentation of drug use and decided not to use Healthy Pregnant as a control group in our research until now.

The use of different data sources as comparator could be conceived as an additional limitation. Specifically for BMI, maternal age and birth-weight, we compared data that were derived on the basis of different methods. Although these comparisons are not perfect, these aspects are not likely to affect the current results and thus would lead to essentially similar conclusions. If we had used the Healthy Pregnant data set as a control group in a case–control study for assessing the risk for drug use on specific congenital malformations, it would result in an overestimation of the risk. In the case of a protective effect study, the opposite would be true with an underestimation of the protective effect. Especially in case of risk factors, it is important not to unnecessarily raise patient worries.

Exposure to drugs in our control sample is reported correctly (and is derived from the same source). However, the use is not comparable and therefore not representative for the use in the population covered by EUROCAT. In the literature, several examples can be found of this type of selection bias in studies using external control groups [16]. Not all of these groups were validated on representativeness before they were used as a control group. Another option might be the use of controls with genetic disorders. In 2007, a study was published comparing the maternal drug use of pregnancy outcomes with genetic disorders and the maternal drug use in the general pregnant population [17]. Once adjusted for maternal age, the use of all tested drug groups with the exception for antimigraine drugs was comparable between both groups.

An advantage of these controls with genetic disorders is that it may reduce both recall and selection bias. However, as for malformed controls, the translation to the general population is not easy because the influence of drugs on genetic outcomes cannot be ruled out [18,19]. Regardless, we believe that in the absence of a representative non-malformed control group, a genetic disorder control group should be considered as an appropriate solution.

For the choice of our control groups, it is more important that exposures to drugs are representative than the fact that the control group consists of non-malformed pregnancy outcomes, especially considering that malformed controls can be used to help reduce recall bias, which is often a problem with retrospective studies like case–control studies. Ideally, one should use both a malformed and a non-malformed control group. For future research, we aimed to identify a better non-malformed control group either by linking to existing data sets or by collecting a new group using another method. However, the results of this evaluation strengthened our belief that a control group is not good simply because it is a non-malformed group.

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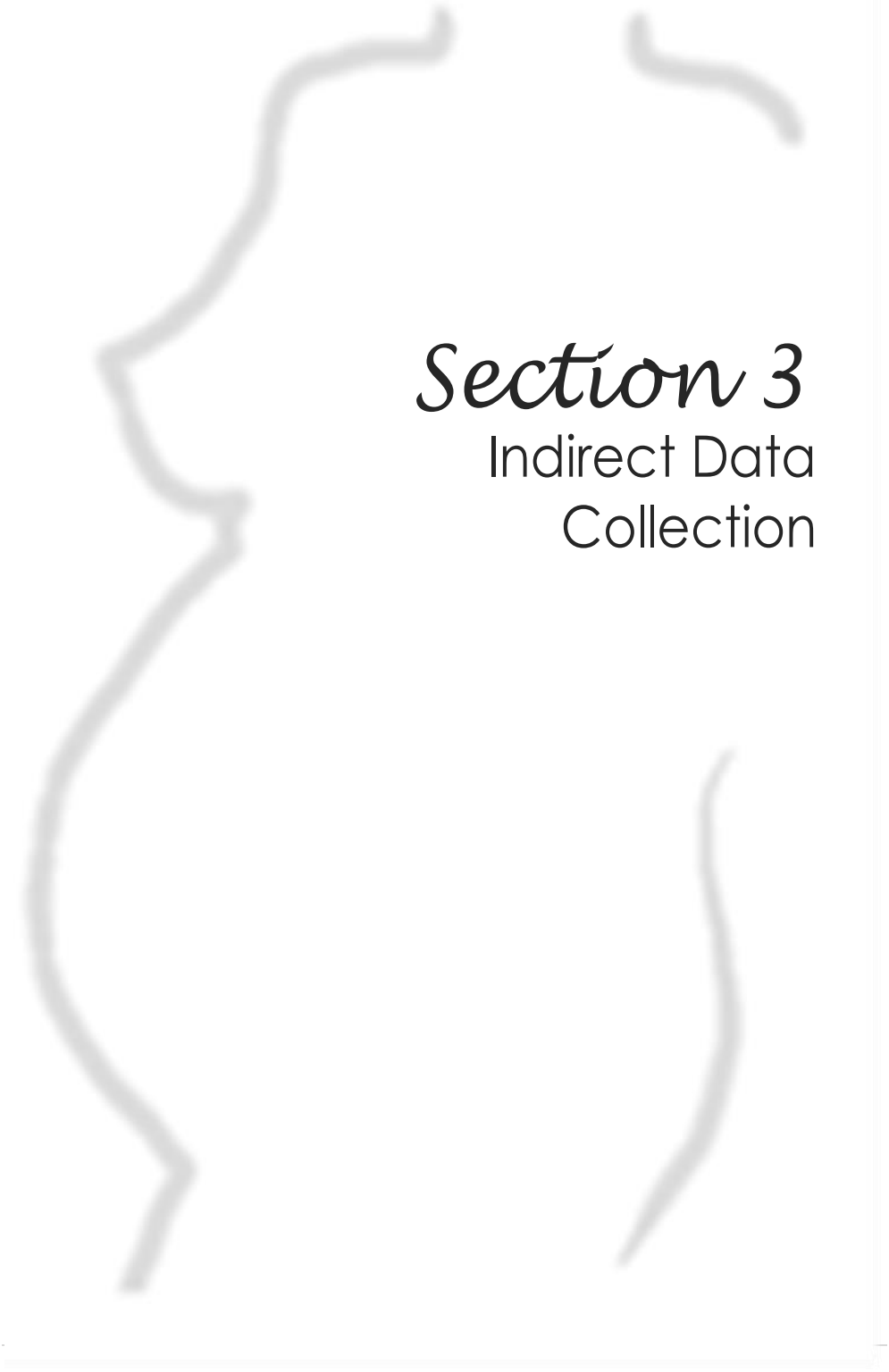

Section 3

Indirect Data Collection

Chapter 3.1 A population analysis of prescriptions for asthma medications during pregnancy.

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Abstract

Background

It is important to control asthma during pregnancy. However, some studies indicate that women stop or change their asthma medications when they become pregnant.

Objective

We used a population database to analyze changes in prescriptions for asthma medications to patients before, during, and after pregnancy.

Methods

We collected information from the pregnancy database that is part of the population-based pharmacy prescription interaction database (IADB.nl) from the Northern Netherlands. Our study cohort comprised 25,709 pregnancies for which prescription data was available. We collected data over a study period of 1 year before pregnancy until 6 months after birth, and analyzed data from pregnant women who received at least 1 prescription for asthma medication during the study period (n=2072), identifying all prescriptions of asthma medication and oral corticosteroids.

Results

Prescriptions for asthma medications did not change during pregnancies from 1994–2003. However, during the period of 2004 to 2009, there was a significant decrease (p=0.017) in prescriptions for asthma medications during the first months of pregnancy, compared to the months before pregnancy, especially in prescription of long-acting bronchodilators. Although most asthma prescriptions continued throughout pregnancy, prescriptions for controller therapies were reduced by 30% during the first months of pregnancy.

Conclusion

Many women stop or reduce their use of asthma medications when they become pregnant. Strategies to safely control asthma during pregnancy are needed.

Introduction

Drug use during pregnancy cannot always be avoided, especially for women with chronic conditions. During the last decades, the prevalence of asthma has increased worldwide; an estimated 3%–12% of pregnant women have asthma [1,2]. Poor control of asthma is associated with maternal and neonatal complications, such as preeclampsia, preterm delivery, and low birth weight, so adequate treatment is important [1,3,4]. However, the safety of many asthma drugs for use during pregnancy has not been determined [5].

The Netherlands has no official, published guidelines about the use of asthma medication during pregnancy [6]. The Dutch College of General Practitioners (Nederlands Huisartsen Genootschap (NHG)) has stated that pregnant women can continue taking short-term β2-adrenergic receptor agonists and the inhaled corticosteroids budesonide and beclometasone. Less is known about the effects of fluticasone during pregnancy, but continuation seems safe. Little is known about the effects of long-acting β2 agonists, anticholinergics, or leukotriene modifiers, so NHG guidelines advise against the use of these medications during pregnancy. In cases of serious exacerbation, the risks of hypoxemia outweigh those of systemic corticosteroids [7].

The Global Initiative for Asthma (GINA), formed in 1993, works with health care professionals and public health officials to reduce asthma prevalence, morbidity, and mortality [8]. Their reports form the bases for many national guidelines [9]. In 2010, they published a report stating "Pregnant women with asthma should be advised that greater risk to their baby lies with poorly controlled asthma and the safety of most modern asthma treatments should be stressed [9]." The US National Asthma Education Program (NAEPP) stated that maintaining adequate control of asthma during pregnancy is important for the health and well-being of mothers and babies. The inadequate control of asthma is a greater risk to the fetus than asthma medication [4]. Nonetheless, many women are concerned about the risks of asthma medications during pregnancy and consider discontinuation [10]. Reduced use of asthma medication during the first trimester of pregnancy was reported by some studies [11,12].

To investigate the continued use of different asthma medications throughout pregnancy, we tracked numbers of asthma prescriptions using a Dutch database. We compared numbers of prescriptions for asthma medication written up to 2003 with those from 2004 to 2009, to identify changes associated with the increased emphasis on the importance of asthma control during pregnancy.

Material and Methods

Database

This study was performed using the pregnancy database that is part of the population-based pharmacy prescription interaction database (IADB.nl). The IADB.nl contains data on prescriptions filled at 55 pharmacies in the Northern Netherlands, covering a population of approximately 500,000 individuals, from 1994 to 2009. Because of the high level of commitment of patients to their pharmacies, the IADB.nl contains an almost-complete medication history for each individual registered. The database contains information on all prescriptions filled, except medications prescribed during hospitalization. Information about over-the-counter drugs is not available. Each prescription contains the code of the drug according to the Anatomical Therapeutic Chemical (ATC) classification [13], along with the date of dispensation, amount dispensed, dose regimen, and the prescriber. Each patient has a unique anonymous identification number, and date of birth and sex are listed.

Pregnancies in the IADB.nl can be identified by connecting every child listed with a female, 15–50 years old, with the same address code, providing there are no other women in this age range with the same address code. Using this method, mothers of 64.9% of children listed in the IADB.nl could be identified. Validation of this method is described elsewhere [14]. The pregnancy period was estimated by subtracting 273 days (3 trimesters of 91 days) from each child's date of birth.

Study population

We analyzed data from pregnancies for which complete data were available from 1 year before the theoretical date of conception until 6 months after birth, and for which the mother had at least 1 prescription of asthma medication during this period. For these pregnancies, we identified all prescriptions of asthma medication (R03) and oral corticosteroids (H02).

Prescription rate was defined as the percentage of all pregnancies with at least 1 prescription of a drug or drug group in a defined period. Differences were tested in R version 2.10.1, using the Pearson's X^2 analysis with Yates's continuity correction. We defined chronic use of a drug, or a drug group as at least 3 prescriptions for that drug or group in the year before pregnancy. We classified asthma drugs into the following categories: short-acting bronchodilators, inhalation corticosteroids, long-acting bronchodilators, combination preparations of an inhalation corticosteroid and a long-acting bronchodilator, and other medications (see Table 1). All but the short-acting bronchodilators are considered 'controller medications'.

Table 1: Number of pregnancies with at least 1 prescription of a drug or group during each time period (Based on data from 25,709 pregnancies in the IADB.nl).

	Months before pregnancy				Months during pregnancy**			Months after pregnancy	
	12–10	9–7	6–4	3–0	0–3	3–6	6–9	0–3	3–6
Short-acting bronchodilators*	**497**	**477**	**485**	**468**	**463**	**470**	**459**	**402**	**428**
Salbutamol	434	415	424	419	418	422	420	365	392
Terbutaline	41	50	44	40	35	31	27	26	30
Ipratropium	31	18	25	16	24	32	28	17	11
Efedrine	1	0	0	0	0	0	0	0	0
Salbutamol oral	0	0	0	0	1	0	1	0	0
Terbutaline oral	1	3	3	0	1	0	0	0	0
Salbutamol + Ipratropium	1	0	0	2	1	1	0	0	0
Inhalation corticosteroids*	**345**	**355**	**328**	**343**	**350**	**369**	**341**	**302**	**330**
Beclometasone	160	157	145	146	229	248	248	169	159
Budesonide	107	115	108	104	81	73	65	79	97
Fluticasone	80	86	78	95	55	53	32	57	77
Ciclesonide	0	0	1	0	0	0	0	0	1
Long-acting bronchodilators*	**62**	**59**	**72**	**56**	**41**	**26**	**29**	**32**	**53**
Salmeterol	29	27	31	27	17	8	10	12	25
Formoterol	27	27	35	24	21	15	14	15	23
Tiotropium	4	6	5	3	1	1	1	2	3
Fenoterol	2	1	3	2	3	3	4	3	4
Fenoterol + Ipratropium	1	0	1	0	1	1	1	1	0
Combination preparations*	**80**	**85**	**95**	**106**	**54**	**42**	**44**	**79**	**102**
Fluticason + Salmeterol	58	59	64	77	35	25	29	53	68
Becl/Bud+ Formoterol	22	26	32	30	19	17	15	26	34
Other medications*	**31**	**26**	**28**	**23**	**16**	**17**	**18**	**17**	**15**
Cromoglicic acid	18	15	17	11	11	13	13	11	9
Montelukast	12	9	9	10	4	2	2	6	5
Theophylline	1	2	2	2	1	2	3	1	1

*Because there can be more than 1 prescription for a drug in each group, numbers do not always add up.

**The months 1-3 of pregnancy refer to the first trimester, months 4-6 to the second trimester and months 7-9 to the third trimester of pregnancy.

For all chronic users of a drug or drug group in the year before pregnancy, it was determined whether they continued taking the same drug or a drug from this group, switched to another asthma medication, or stopped taking asthma medication in the first trimester of pregnancy. We used chronic use of asthma controller therapy (at least 3 preparations of controller medication in the year before pregnancy) as a proxy for actual asthma.

Results

The study cohort comprised 25,709 pregnancies for which prescription data were available during the study period (from 1 year before until 6 months after pregnancy). Of these pregnancies, 2072 (8.1%), in 1695 women, had at least 1 prescription of asthma medication during the study period, including 55 twin pregnancies and 1 triplet pregnancy. The women were of a mean age of 30.0 years old (range 15–48 years) when they gave birth after the 2072 pregnancies. In 52 of the pregnancies (2.5%), the woman was 40 years or older. Table 1 shows the asthma medication (ATC: R03) that was prescribed to the study population during the study period.

Figure 1: Classification of asthma drug use during pregnancy

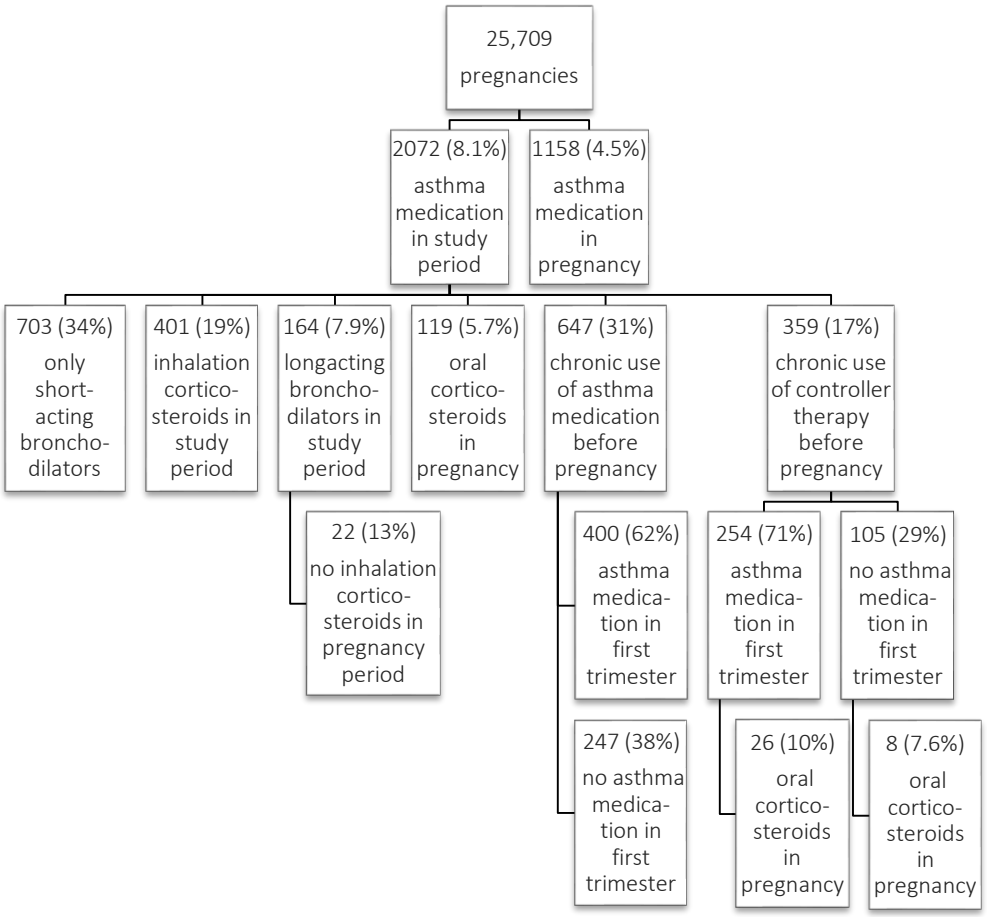
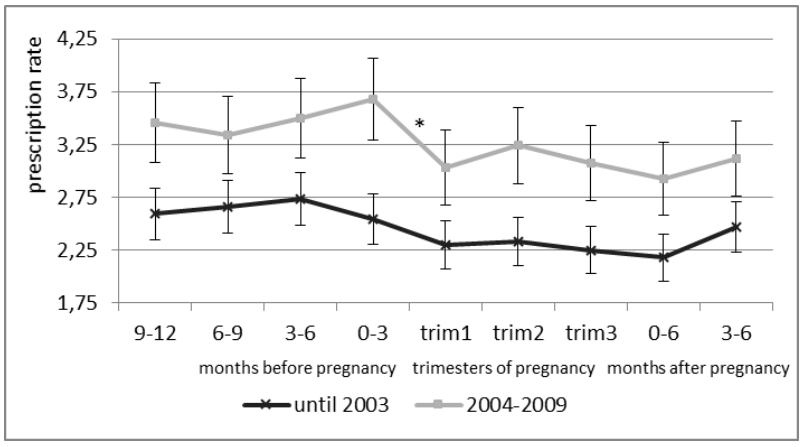


Figure 1 shows the classifications of the prescription rates. Of the 2072 pregnancies prescribed asthma medication during the study period, 703 (33.9%) received prescriptions for short-acting medication only, 401 (19.4%) received at least 1 prescription of oral corticosteroids, and 119 (5.7%) had at least 1 prescription for an oral corticosteroid during pregnancy, indicating an exacerbation. Long-acting bronchodilators were prescribed during 164 pregnancies (7.9%); 22 of these (13.4%) received no additional inhalation corticosteroids.

Figure 2 compares the prescription rate through the end of 2003 with the rate from 2004 to 2009. From 2004 to 2009 more asthma medication was prescribed than in the period through 2003 ($p<0.001$). During the period of 2004 to 2009, there was a significant decrease ($p=0.017$) in prescriptions for asthma medication in the first trimester of pregnancy, compared with the 3 months before pregnancy. In the period though 2003 there was no significant decrease in asthma medication use during the first trimester. Figure 3 compares the prescription rates for the main groups of asthma medications during different stages of the study period, until 2003 and from 2004 to 2009.

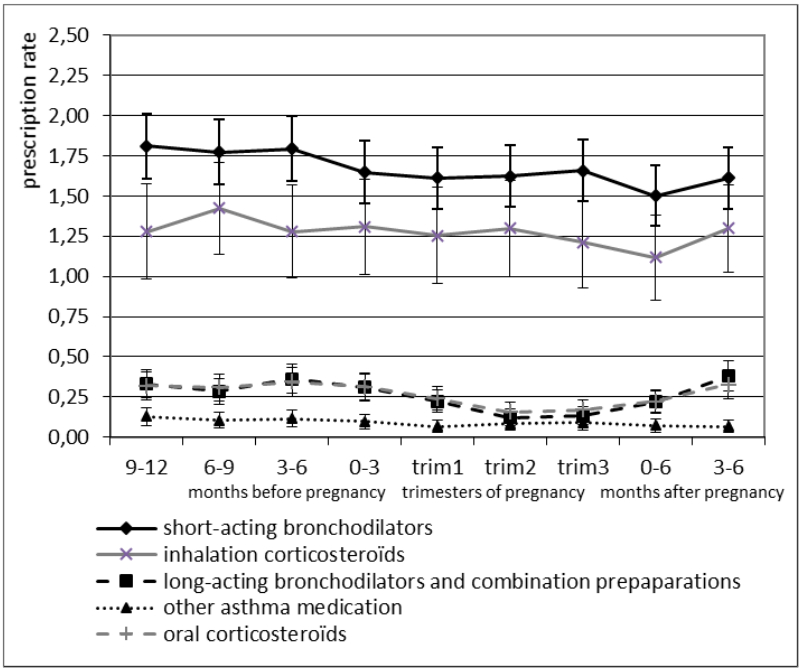
In the period until 2003 (Figure 3a), there was fluctuation in the prescription rates of the different groups of asthma medications over the study period, but no changes were statistically significant. From 2004 to 2009 (Figure 3b), there was a significant decrease in prescription rates of long-acting bronchodilators and combination preparations from the months before pregnancy to the first months of pregnancy ($p<0.001$). There was then a significant increase in prescription rates of these drugs from last months of pregnancy to the first months after pregnancy ($p=0.029$).

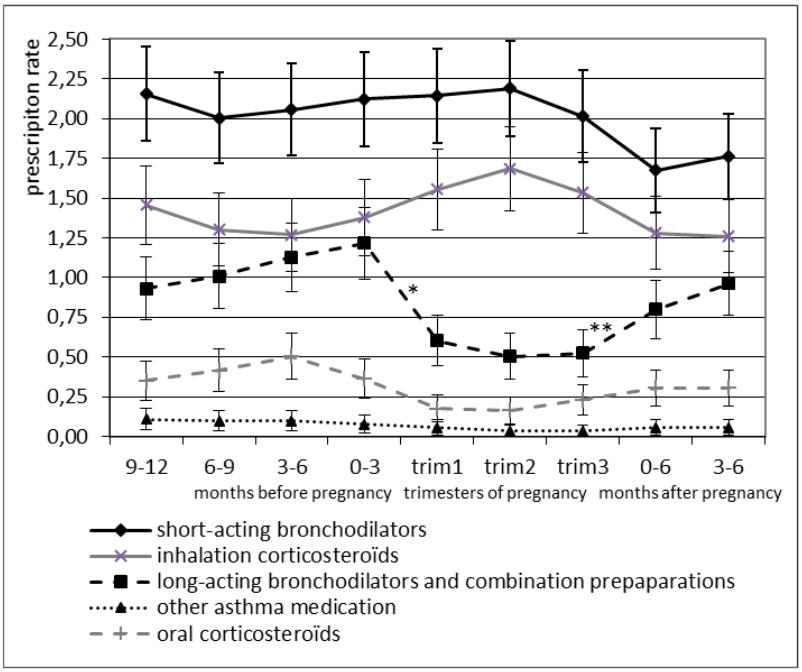
Figure 2: Prescription rate during the study period



* significant decrease in prescription rate (p = 0.017)

Figure 3a: Prescription rate of the main groups of asthma medications until 2003.
Figure 3b: Prescription rate of the main groups of asthma medications from 2004 to 2009.





* significant decrease (P<0.001)
** significant increase (P=0.029)

The decrease in prescription rate of long-acting bronchodilators during the first few months of pregnancy, from 2004 to 2009, was observed for groups of women younger and older than 31 (data not shown). However, among women 31 years and older, the decrease was compensated by an increased prescription rate of short-acting bronchodilators and inhalation corticosteroids (data not shown). The prescription of inhalation corticosteroids tends to increase during pregnancy, but this increase observed was not statistically significantly.

Table 2 shows the change in prescriptions during the first trimester of pregnancy among women who consistently used asthma drugs (at least 3 prescriptions) of each category in the year before pregnancy. Most asthma prescriptions continued throughout pregnancy. When regular asthma medication was changed to an inhalation corticosteroid during pregnancy, it was usually switched to beclometasone; there were only a few changes to budesonide. Within the class of inhalation corticosteroids, there was a switch to beclometasone in the first trimester of pregnancy for 16 of 62 pregnancies (25.8%) with at least 3 prescriptions of fluticasone in the year before pregnancy and none to budesonide (not in table).

Table 2: Change in prescriptions during first trimester of pregnancy vs year before

	Any asthma medication (ATC R03) n(%)	Short-acting broncho-dilators n(%)	Inhalation cortico-steroids n(%)	Long-acting broncho-dilators n(%)	Combination preparations n(%)	Other asthma medication n(%)
Chronic users of drugs in the year before pregnancy	647	319	231	52	74	24
Patients that continued		203 (63.6%)	122 (52.8%)	22 (42.3%)	32 (43.2%)	12 (50.0%)
Change to:						
beclometasone				12 (23.1%)	11 (14.9%)	2 (8.3%)
budesonide				3 (5.8%)	2 (2.7%)	0
short-acting bronchodilators			2 (0.9%)	6 (11.5%)	8 (10.8%)	0
Patients that stopped taking the drug	247 (38.2%)	93 (29.2%)	61 (26.4%)	8 (15.4%)	18 (24.3%)	5 (20.8%)

Of 647 pregnancies with at least 3 prescriptions of asthma medication during the year before pregnancy, 247 (38.2%) did not have a prescription for any asthma medication during the first trimester of pregnancy.

Of all pregnancies defined to have asthma (3 or more prescriptions for a controller medication in the year before pregnancy, n=359), 105 (29.2%) did not have a prescription for any asthma medication during the first months of pregnancy (Figure 1). There was no statistical difference in numbers of pregnancies with at least 1 prescription for oral corticosteroids during pregnancy between pregnancies with or without prescriptions of asthma medication during the first trimester of pregnancy ($p = 0.44$).

Discussion

This study shows a significant increase in prescriptions for asthma medications among pregnant women in the period from 2004 to 2009, compared to the period before 2004. The increase was greatest for long-acting bronchodilators and combination preparations (Figures 3a and 3b). The increase in prescriptions of asthma medications was likely due to the increasing prevalence and awareness of asthma [1,2]. Long-acting bronchodilators and combination preparations are relatively new agents that have been increasingly prescribed since 2000 as add-on therapies to inhalation corticosteroids.

Despite their understanding of the importance of adequate asthma-control, many women stop their controller therapy when they become pregnant. We observed a significant decrease in prescription of asthma medications during the first trimester of pregnancy in the period from 2004 until 2009, especially for long-acting bronchodilators, either as separate preparations or in combination with inhaled corticosteroids. This group contains relatively new agents, and their safety during pregnancy has not been established.

The NHG standard advises against use of this medication during pregnancy [7], but the GINA guidelines and the NAEPP stress the importance of controlling asthma, even when the safety of medications has not been proven [4,9]. A long-acting bronchodilator is usually added to therapy with an inhalation corticosteroid when a medium dose of inhalation corticosteroids fails to achieve adequate control (Table 3). So long-acting bronchodilators are usually prescribed for patients with more severe asthma and discontinuation could lead to severe symptoms of respiratory distress.

Almost 30% of pregnancies that consistently used controller therapy for asthma in the year before pregnancy did not have a prescription for any asthma medication during the first trimester of pregnancy. This might be partly due to the fluctuating course of asthma.

Blais et al. and Enriquez et al. reported decreased use of short-acting bronchodilators and inhalation corticosteroids in the first trimester of pregnancy, based on data until 2000 and 2001 respectively [11,12]. However, long-acting bronchodilators were not yet commonly used during these time periods.

In a study of drug prescription patterns in the Netherlands, Bakker et al. found that most drugs for chronic conditions were prescribed less during pregnancy. In the months after pregnancy, prescription rates increased, but not to pre-pregnancy levels, most likely because of breastfeeding. The prescription rate of asthma medication, alternatively, decreased slightly in the months after pregnancy, like we observed [15] (Figure 2). Engeland et al. also showed a decrease in the prescription of asthma medication during the first trimester of pregnancy and another in the 3 months after pregnancy in Norway [16], as did Malm et al. in a study of prescription drug use during pregnancy and lactation in Finland [17].

Of the women that no longer received prescriptions for long-acting bronchodilators or combination preparations when they became pregnant, more than 10% who did not have a prescription for a short-acting bronchodilator before pregnancy did have one during pregnancy, indicating a worsening of symptoms and less asthma control. Women who stopped controller therapy when they became pregnant appeared to be prone to exacerbations.

Post-partum, asthma usually returns to pre-pregnancy state within 3 months [18], so an increase to pre-pregnancy prescription levels would be expected, with a possible delay due to women's reluctance to use medications during breastfeeding. We observed prescription of asthma medication to return to pre-pregnancy levels within 6 months after birth (Figure 2).

Inhalation corticosteroids are the drugs of choice to treat persistent asthma (Table 3). Women with asthma who, upon becoming pregnant, stopped their prescription for their usual controller medication and received a prescription for another drug, were most likely to switch to beclomethasone, only a few changed to budesonide (both are inhalation corticosteroids) (Table 2). Guidelines often state that budesonide is the first choice of inhalation corticosteroid for pregnant women, because this drug has the most data available [4,9]. In the Netherlands, beclomethasone is the inhalation corticosteroid of first choice for pregnant patients [19].

Long-acting bronchodilators are only to be used for the treatment of asthma when they are combined with an inhalation corticosteroid, because the long-acting bronchodilators do not affect airway inflammation. This drug is added to therapy when asthma is not controlled by inhalation corticosteroids [7,9]. However, in our study population, 14.4% of all pregnancies with at least 1 prescription for a long-acting bronchodilator had no prescriptions for inhaled corticosteroids during the study period (1 year before to 6 months after pregnancy). This is not a correct treatment strategy.

If health care practitioners do not prescribe inhalation corticosteroids, there are effective alternatives, including monotherapy with leukotriene modifiers or theophylline [4,7,9].

Table 3: Asthma Severity and Strategy for Treatment [4,7]

Asthma severity	Treatment step	Symptoms	Preferred treatment
Intermittent	Step 1	≤ twice a week	A short acting bronchodilator, as needed.
Mild persistent	Step 2	> twice a week	Low dose of inhalation corticosteroids, to be increased to a medium dose if symptoms are not controlled sufficiently. A short acting bronchodilator, as needed.
Moderate persistent	Step 3	Symptoms not sufficiently under control with step 2 medication	Medium dose of inhalation corticosteroids and a long-acting inhaled bronchodilator. A short acting bronchodilator, as needed.
Severe persistent	Step 4	Symptoms not sufficiently under control with step 3 medication	High dose of inhalation corticosteroids and a long-acting inhaled bronchodilator and corticosteroid tablets if needed. A short acting bronchodilator, as needed.

Study Strengths and Limitations

For our study population, complete data were available on all asthma medication prescribed in the period from 1 year before until 6 months after pregnancy. We compared prescriptions during the period before pregnancy with those during pregnancy, so each woman served as her own control. However, this study has certain limitations. Because the IADB.nl only contains prescription data, it is not known whether the medication was actually taken.

This could lead to an overestimation of drug use. Also, asthma medication is often taken as needed, and used for a long period after it was prescribed, which could result in underestimations of drug use. Furthermore, the IADB.nl has no information about medication prescribed during hospitalization, which could lead to an underestimation of exacerbations and medications prescribed.

We do not have information about the indication for each prescription. This could lead to overestimations of asthma cases and exacerbations. Oral corticosteroids, for example, can be prescribed for a number of indications other than asthma. Also, 2.5% of the pregnancies in the study were in women 40 years or older, so some cases that we considered to be asthma might actually have been chronic obstructive pulmonary disease.

Anti-histamines are often prescribed to patients with asthma who also have allergic rhinitis [20]. Anti-histamines are prescribed for many allergic symptoms as well as for nausea and vomiting, which is a common problem during the first months of pregnancy. Because we did not have information about indications, we did not analyze data on prescriptions for anti-histamines.

We used 273 days - the mean length of gestation - to calculate dates of conception pregnancy, and months after birth. Some periods might therefore have been misclassified, and actual differences between trimesters might have been underestimated. Furthermore, the IADB.nl only includes information about live births—data on abortions, miscarriages, and stillbirths are not included. A pregnancy is only identified when the child is dispensed a prescribed drug and can be coupled to a mother.

Since we have had no contact with the women included in the study or their physicians, it is unclear whether decisions to discontinue or change prescriptions were made by the pregnant women or their physicians. Even pharmacists can be involved in changing prescriptions.

Our study covers a long period (from 1994 until 2009), during which the importance of adequate control of asthma during pregnancy has gained attention. We did not see an improvement in the continuation of asthma prescriptions throughout pregnancy when we compared the period up to 2003 with the period 2004 to 2009.

A study of perceptions of asthma treatment during pregnancy by Chambers, found that only 19% of participating women had discussed the need to continue taking their asthma medication if they would be pregnant with their physician [10]. Thirty nine percent of women who became pregnant reduced their asthma medication, and a third of these did so without discussing it with their physician. But many women would change their minds if given accurate information about the risks of their medications, or if continuation was recommended by their care giver [10]. Patients and even doctors tend to overestimate the risks of most medication during pregnancy [21]. So for women to make the right decision about their asthma medication before they become pregnant, they should be thoroughly informed about its risks and benefits. A recent study by Lim et al. found that 26% of general practitioners who responded to a survey would stop or reduce the dosage of controller medication when a patient became pregnant, even though her asthma was well controlled [22]. Physicians should keep up to date on the latest research findings about continuation of asthma medications during pregnancy, and explain these to patients who might become pregnant.

In conclusion

Almost 30% of women with asthma stop their controller therapy when they become pregnant. This can lead to poor control of asthma, and increase risk of exacerbations, along with risk of maternal and neonatal complications. There is room for improvement in treating asthma in pregnant women, which could lead to better health and care for mothers and children.

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Chapter 3.2 Maternal high-dose folic acid during pregnancy and asthma medication in the offspring.

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Abstract

Purpose

Low dose folic acid supplementation (0,5 mg) taken during pregnancy has been associated with an increased risk for childhood asthma. The effect of high dose folic acid (5 mg) advised to women at risk for having a child with a neural tube defect, has not been assessed so far. Our aim was to investigate the effect of dispensed high dose folic acid during pregnancy and asthma medication in the offspring.

Methods

We used data from the pregnancy database IADB.nl, which contains pharmacy-dispensing data of mothers and children from community pharmacies in The Netherlands from 1994 until 2011. The dispension of asthma medication in children exposed in utero to high dose folic acid was compared to children who were not exposed to this high dose. Incidence Rate Ratio's (IRR) with 95% confidence intervals (CI) were calculated.

Results

In 2.9% (N= 913) of the 39,602 pregnancies in the database the mother was dispensed high dose folic acid. Maternal high dose folic acid was associated with an increased rate of asthma medication among children: recurrent asthma medication IRR=1.14 (95%CI: 1.04-1.30), recurrent inhaled corticosteroids IRR=1.26 (95%CI: 1.07-1.47). Associations were clustered on the mother and adjusted for maternal age, maternal asthma medication and dispension of benzodiazepines during pregnancy.

Conclusion

Almost 3% of the children were prenatally exposed to high dose folic acid. This study suggests that supplementation of high dose folic acid during pregnancy might increase the risk of childhood asthma.

Introduction

Women are advised to increase their intake of folic acid 4 weeks before conception until 8 weeks after by taking a supplement. Although folic acid supplementation during this period has been shown to decrease the occurrence of neural tube defects (NTDs) and other birth defects [1,2], there have been concerns about the long term health effect for the offspring [3-6]. A health outcome that has been linked to prenatal folic acid supplementation is childhood asthma. Children exposed to maternal folic acid supplementation during prenatal life may have an increased risk to develop asthma during childhood. Observational studies in humans showed an increased risk for asthma symptoms in young children after prenatal exposure to maternal folic acid supplementation [7-9], but not all studies confirmed this [10-12]. These observations were paralleled by an experimental study in mice that suggested a more severe allergic lung inflammation in offspring of mice that had been exposed to a maternal diet high in folic acid compared to non-exposed mice [13]. These adverse effects of folic acid are thought to be caused by epigenetic modifications, because folic acid plays a key role in DNA methylation [14]. Epigenetic modifications do not change the DNA sequence, but refer to alterations in the accessibility of the DNA and thereby gene expression.

The current evidence regarding the effect of folic acid on the development of childhood asthma is based on studies using a normal dietary intake or prenatal folic acid supplement use of the regular dose (0.4-0.5 mg). No studies so far investigated the asthma risk among children exposed to high dose folic acid supplementation of 4-5 mg during pregnancy, which is indicated in specific subgroups of women. According to international and Dutch guidelines, women who previously had a child with a NTD or were born with a NTD themselves are recommended to take this high dose of folic acid [15,16]. In addition, women using folic acid antagonists, like antiepileptic drugs, women at risk for developing anaemia and women who have developed anaemia may receive a prescription for high dose folic acid [16-18]. While folic acid supplements of a regular dose are available over the counter, supplements containing a high dose folic acid are obtained by a prescription from a medical doctor. In the Netherlands and other countries within the EU there is no mandatory fortification of foods with folic acid.

Children of mothers who used a tenfold increased folic acid supplementation during pregnancy may in particular be at risk for the adverse effect of prenatal exposure to folic acid, but there is hardly any information about the dispension of this high dose folic acid during pregnancy.

Therefore, in this study we will assess the prevalence and determinants of high dose folic acid dispension among pregnant women and investigate the incidence of asthma medication among children of mothers who filled a prescription for high dose folic acid supplementation during pregnancy.

Methods

Study population

For this study, we used data from the IADB.nl, a population based pharmacy prescription database [19]. This database contains pharmacy-dispensing data from about 55 community pharmacies in the Netherlands. Because Dutch patients usually register at a single community pharmacy an almost complete medication history of a subject's prescribed drugs is available [20]. The use of over the counter drugs and in-hospital prescriptions are not included. The database covers a population of approximately 500,000 persons from 1994 until 2011 and has been used before in this type of prevalence and association studies [21]. The IADB.nl contains a separate pregnancy database where the medication history of a mother can be linked to the pharmacy record of her child, by linking a child in the database to the only women aged 15-50 years with the same address code. Fathers can be linked to the child this way as well. A validation study showed that by this method 65% of the mothers could be identified, with 99.4% of them linked correctly [22]. Since gestational age at birth is unknown, the theoretical pregnancy period was estimated by subtracting 273 days (3 trimesters of 91 days) from a child's date of birth.

Since high dose folic acid supplements are obtained by a prescription of a medical doctor, it is recorded in this database. Every child has been allocated a personal number and this also applies for twins, triplets etc. When there is a multiple pregnancy, the pregnancy itself can be counted as one, but the mother-child relations can also be assessed separately for analyses. For this study, all mother-child relations from the pregnancy database from 1994 until 2011 were used to assess the association between high dose folic acid dispension during pregnancy and the dispension of asthma medication in the offspring. For the calculation of the prevalence of dispensed high dose folic acid and the development in time, pregnancies with a date of birth from 1998 until 2009 were used, because for the earlier years little data was available and for the later years not all pregnancies have been identified yet.

We calculated the prevalence of dispensed high dose folic acid for the three months before pregnancy, the three trimesters of pregnancy, the first three months after pregnancy and the period of 3-6 months after pregnancy. Because only de-identified and pre-existing data were used, ethical approval was not needed for this study.

Exposure and outcome definition

Exposure to maternal high dose folic acid was defined as: at least one dispension of high dose folic acid during pregnancy (coded according to the WHO classification system with the anatomical therapeutically chemical (ATC) code: B03BB01 and based on preparation dispensed (folic acid 5 mg) or the number of defined daily doses prescribed and the number of days prescribed for). The reference group consisted of all women who were not dispensed high dose folic acid during pregnancy.

Dispension of asthma medication for the child was taken as a proxy for childhood asthma. A list of all asthma medication dispensed to children in the IADB.nl pregnancy database is shown in Supplementary Table 1 (Appendix 4). Four outcome parameters were defined: 1) at least one dispension of any asthma medication (ATC-code R03), 2) at least two dispensions of any asthma medication, 3) at least one dispension of an inhalation corticosteroid (ICS, ATC-code R03BA) and 4) at least two dispensions of inhalation corticosteroids.

Statistical analyses

The prevalence of dispensed high dose folic acid was calculated by taking the number of pregnancies where the mother was dispensed high dose folic acid at any time during pregnancy compared to the total number of pregnancies. The incidence rate (IR) for the four defined outcome parameters was calculated by determining the number of cases per time at risk (in years). Time at risk was defined as the period from day of birth until either the first dispension date or the last date the child was registered in the database, whatever occurred first. Crude and adjusted incidence rate ratio's (IRR) and 95% confidence intervals (CI) were calculated for the exposure compared to the reference group. As possible confounders we took into account: age of the mother, single or multiple pregnancy, maternal asthma medication and paternal asthma medication. In addition confounding by medication associated with high dose folic acid supplementation was evaluated.

We assessed dispension of iron supplements, anti-folate medication (antiepileptics, sulphonamides and trimethoprim), antidepressants, antihypertensives, antidiabetics and benzodiazepines during pregnancy, because prenatal exposure to these drugs or to the underlying condition might possibly be related to the development of childhood asthma and may confound the association [23]. The IRRs were adjusted for all factors (listed in Table 1) that were significantly different for women that were dispensed high dose folic acid during pregnancy and women that were not and for children with and without dispensed asthma medication. Since part of the mothers were present in the database with more than one pregnancy, analyses were clustered on the mother.

Table 1: Differences in study characteristics for exposure vs no exposure to high dose folic acid during pregnancy and childhood asthma medication fill vs no asthma medication fill (N children=35604).

Variable	High dose folic acid during pregnancy (n=1308) n(%)	No high dose folic acid during pregnancy (n=34,296) n (%)	p-value	Children with asthma medication (n=11,780) n (%)	Children with no asthma medication (n=28,848) n (%)	p-value
Gender child (% female)	710 (48.6)	18,828 (48.1)	0.91	4,826 (41.0)	14,712 (51.0)	<0.001
Mean maternal age (sd)	**31.0 (4.7)**	**30.4 (4.7)**	**<0.001**	**30.1 (4.6)**	**30.5 (4.7)**	**<0.001**
Multiple pregnancy	618 (42.3)	1,398 (3.2)	<0.001	558 (4.7)	1,458 (5.1)	0.18
Dispension of asthma medication mother in the year before or during pregnancy	**116 (7.9)**	**2,581 (6,6)**	**0.04**	**1,191 (10.1)**	**1,506 (5.2)**	**<0.001**
Dispension of asthma medication to the father	173* (18.4)	4,200** (18.7)	0.81	1764*** (23.7)	15,984**** (16.3)	<0.001
Prescription of iron supplements during pregnancy	1,193 (81.7)	12,963 (33.1)	<0.001	4,071 (34.6)	10,084 (35.0)	0.45
Prescription antiepileptics during pregnancy	62 (4.2)	82 (0,2)	<0.001	41 (0.3)	103 (0.4)	0.89
Prescription antifolate antibiotics during pregnancy	20 (1.4)	651 (1.7)	0.39	249 (2.1)	422 (1.5)	<0.001
Prescription of anti-hypertensives during pregnancy	150 (10.3)	829 (2,1)	<0.001	289 (2.5)	690 (2.4)	0.71
Prescription of antidepressants during pregnancy	60 (4.1)	735 (1.9)	<0.001	240 (2.0)	555 (1.9)	0.45
Prescription of antidiabetics during pregnancy	22 (1.5)	326 (0.8)	0.006	99 (0.8)	249 (0.9)	0.82
Prescription benzodiazepines during pregnancy	**88 (6.0)**	**1,098 (2.8)**	**<0.001**	**390 (3.3)**	**796 (2.8)**	**<0.01**

*Ntotal = 829; **Ntotal = 19,633; ***Ntotal = 7437; ****Ntotal = 15984

ATC-codes used to determine exposure are listed in Supplementary Table 2 (Appendix 4). Differences between the exposed and reference group were tested at a level of significance of 0.05, using the students t-test for maternal age and the Pearson's Chi-squared test for the other possible confounding factors.

Analyses were stratified on maternal asthma medication, maternal iron supplements during pregnancy and maternal age (30 years of age and younger vs over 30 years of age) and tested the interaction with high dose folic acid prescription by adding the interaction term to the regression model used to assess the possibility of effect modification by these characteristics. To investigate the influence of exposure period on the association between high dose folic acid and childhood asthma , we assessed the association between high dose folic acid and the outcomes separately for the first trimester, the third trimester and the first three months after pregnancy. Since the diagnosis of asthma is difficult in young children and the diagnosis becomes more certain at school age, IRRs were also calculated for children aged 8 years and older as a sensitivity analyses. All analyses were performed using SPSS 18.0 (SPSS, Chicago, IL) or R 3.0.2.

Results

Prevalence and determinants of high dose folic acid supplement prescription

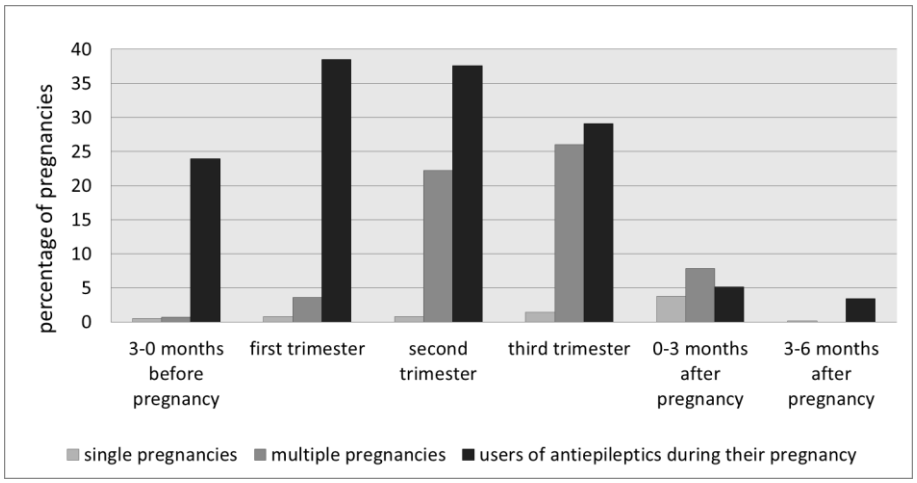
Our study population consisted of 39,602 pregnancies, containing 38,612 single and 990 multiple pregnancies, leading to 40,628 identified children born between 1994 and 2011. For prevalence calculation 32,016 pregnancies with birth date from 1998 - 2009 were included. In 2.9% (N=913) of all pregnancies high dose folic acid was dispensed at any time during pregnancy. Prevalences are presented in Table 2.

Table 2: Prevalence of high dose folic acid prescription between 1998 - 2009 (N pregnancies=32016)

	Prevalence in study population		
Variable	%	n	
High dose folic acid prescription during pregnancy	2.85	913	
Being: Single pregnancies	73.6	672	
Women prescribed antiepileptics	8.3	56	
Multiple pregnancies	26.4	241	
Women prescribed antiepileptics	0.8	2	
Timing of high dose folic acid prescription			*No folic acid in periods before*
Three months before pregnancy	0.52	165	
First trimester	0.87	277	167 (60.2%)
Second trimester	1.25	401	278 (69.3%)
Third trimester	1.99	638	352 (55.2%)
First three months after pregnancy	3.84	1229	1095 (89.1%)
Three to six months after pregnancy	0.15	47	9 (19.1%)

The dispension of high dose folic acid increased with the progression of pregnancy with a peak just after pregnancy . In 88.2% (N=1081) of pregnancies with dispensed high dose folic acid in the three months after pregnancy, prescription took place in the first week after birth. In the three months before pregnancy folic acid was dispensed in 0.5% (N=165) of pregnancies. No change in the prevalences of high dose folic acid dispension was observed from 1998 to 2009 (data not shown).

Figure 1: Percentage of pregnancies from 1998 - 2009 where the mother was dispensed high dose folic acid per trimester and per user group.



In Figure 1 percentages of high dose folic acid dispension per trimester are displayed separately for single pregnancies, multiple pregnancies and pregnancies with prescriptions for antiepileptics. While in single pregnancies dispension of high dose folic acid has its peak after pregnancy, in multiple pregnancies high dose folic acid is dispensed predominantly in the second and third trimester. Antiepileptics were dispensed in 0.4% (N=117) of pregnancies. 23.9% (N=28) of these women started with high dose folic acid before pregnancy with a peak of 38.5% (N=45) in the first trimester of pregnancy.

Association between maternal high dose folic acid prescription and offspring asthma medication

Table 3 shows the crude and adjusted IRRs with 95%CIs for the four different outcome parameters in relation to high dose folic acid dispension during pregnancy. The IRR attenuated only slightly after clustering and adjustment for confounding factors. The risk for asthma medication after exposure to maternal high dose folic acid during pregnancy increased up to 26% for the recurrent dispension of ICS (adjusted IRR=1.26, 95%CI=1.07-1.47).

In all strata the increase in risk was apparent (data are shown in Supplementary Table 3, Appendix 4). No significant interaction between folic acid dispension and maternal asthma medication, maternal iron supplements, maternal age and single/multiple pregnancies respectively was detected. Timing of folic acid use during pregnancy did not seem to have a significant effect on the associations studied. High dose folic acid only dispensed in the first trimester of pregnancy (n=176) and high dose folic acid only dispensed in the third trimester (n=563) versus no dispension, both showed an increased but non-significant risk for recurrent ICS, respectively IRR=1.37, 95%CI=0.91-2.06 and IRR=1.27, 95%CI=0.99-1.63.

High dose folic acid only dispensed in the first three months after delivery versus no dispension also showed an increased asthma risk, but only among women with no additional iron supplementation: IRR=1.44, 95%CI=1.19-1.76. When only children aged 8 years and older were included in the analyses, the adjusted IRR clustered on the mother for maternal high dose folic acid was 1.34 (95%CI=1.07-1.68) for any asthma medication, 1.36 (95%CI=1.05-1.75) for recurrent asthma medication, 1.39 (95%CI=1.05-1.83) for any ICS and 1.36 (95%CI=1.00-1.85) for recurrent ICS.

Table 3: Association between maternal high dose folic acid prescription and asthma medication for the child (N=35604).

No prescription high dose folic acid during pregnancy				Prescription high dose folic acid during pregnancy				Crude association		Adjusted and clustered association*	
%	n	TAR** (years)	IR#	%	n	TAR** (years)	IR#	IRR#	95% CI	IRR#	95% CI
Any prescription asthma medication											
29.0	11344	196986	0.058	31.6	436	7148	0.061	1.06	1.96-1.17	1.03	0.92-1.16
Recurrent prescription any asthma medication											
19.6	7674	201997	0.036	21.9	320	7622	0.042	1.15	1.03-1.29	1.14	1.00-1.30
Any prescription ICS§											
16.7	6552	220024	0.030	19.6	286	7898	0.036	1.22	1.08-1.37	1.22	1.06-1.40
Recurrent prescription ICS§											
12.1	4721	227869	0.021	14.7	215	8208	0.026	1.26	1.10-1.45	1.26	1.07-1.47

* Adjusted for: maternal age, dispension of benzodiazepines during pregnancy, and maternal dispension of asthma medication.

** Time at risk

IR=Incidence Rate; IRR=Incidence Rate Ratio; 95%CI=95% Confidence Interval

§ Inhalation corticosteroids

Discussion

The results of this study show that 2.9% of Dutch pregnant women with a child born between 1998 -2009 were dispensed high dose folic acid at any time during pregnancy. Children of women were dispensed high dose folic acid had a significantly higher risk for dispensed asthma medication during childhood. The risk for recurrent dispension of inhalation corticosteroids increased with 26%.

The prevalence of the observed high dose folic acid dispension (N=913) well exceeded the number of mothers that previously had a child affected by an NTD.

According to EUROCAT NNL, the registry on congenital birth defects that covers approximately the same area as the IADB.nl, the prevalence of isolated NTDs in the Northern Netherlands from 2000-2009 was 0.1%, which corresponds to about 17 children per year [24]. Another reason for prescribing high dose folic acid is the use of antiepileptic medication. If a woman on antiepileptic medication wishes to become pregnant, it is recommended that her blood folate level is tested and folic acid 5 mg is only to be prescribed when blood folate levels are low [16]. Our data shows that 43.3% of the women on antiepileptic medication in the first trimester of pregnancy were dispensed high dose folic acid. We have no data on whether these women were tested on low blood folate.

High dose folic acid may also be prescribed for treatment of anaemia [17]. This could explain the increase in prescription prevalence among single pregnancies with progression of pregnancy and the peak just after delivery for women losing an excess of blood during childbirth. Women at risk for developing anaemia, i.e. women pregnant with multiple children, may also receive a prescription for high dose folic acid for the prevention of anaemia. Although this preventive measure is not advocated in the guidelines it appears to be common practice based on our results.

Since the IADB.nl database contains follow-up data for over 39,000 mothers and children, the database is well suited and has sufficient power to study the effect of an exposure with a low prevalence like high dose folic acid prescription. An important limitation of a prescription database is that it is not known whether and for how long a prescribed drug was actually taken, possibly leading to an overestimation of high dose folic acid use and underestimation of the actual effect on asthma. We do not have information about the indication for the prescription of asthma medication and have no information on asthma symptoms, therefore we will not be able to estimate the amount of possible misclassification. However, recurrent prescription of ICS is indicative for serious respiratory complains and is often prescribed for treatment of childhood asthma. Since the IRR increased with a more stringent outcome definition and was also increased among children from 8 years of age, we interpret our data so that the outcomes resemble asthma and not just respiratory symptoms caused by viral infection.

Since we do not have information about actual gestational age at birth and estimated a theoretical gestational age, some misclassification of the pregnancy period and the different trimesters may have occurred. The IADB.nl does not contain information about maternal characteristics like smoking, socio-demographic factors or maternal diseases. Since we could not take possible confounding by these factors into account some residual confounding may be present, although we have no indication that these factors are related to high dose folic acid prescription.

Another constraint is that the IADB.nlhas no information about medication prescribed during hospitalization. A pregnancy may have been missed because a pregnancy is only identified when the child is dispensed a prescribed drug. Although these limitations may have led to an underestimation of medications prescribed, the results are probably not affected since the missing data are not related to high dose folic acid prescription. Dispensions at another pharmacy than the one a patient is registered in first instance will have an effect on the prevalence rates found, but in the Netherlands, patients usually register at a single community pharmacy and collect all their medication there. We have no indication that this will have any effect on the association found.

Confounding by indication is an important bias to consider. As stated before, the IADB.nl has no information about maternal disease. We can only use dispensed medication as a proxy for maternal disease as described in the methods. Adjusted associations and stratified analyses showed very similar findings, but residual confounding cannot be excluded.

The observation that folic acid supplementation in the direct period after child birth increased the risk for asthma medication, but only in women without additional iron supplementation, is remarkable. We hypothesize that this increased asthma risk is caused by confounding by complications during delivery, because these have been associated with an increased asthma risk [25]. A prescription for high dose folic acid without iron supplement could refer to women at risk for anaemia due to excessive blood loss caused during child birth but who are still immobile and have defecation problems or haemorrhoids. Since we do not have medical information on delivery, the association between the prescription of high dose folic acid after birth without iron supplementation and complications during child birth could not be confirmed.

We found no evidence that high maternal folic acid intake is transmitted to the child by an increase in the level of folic acid in human milk. Moreover, maternal blood folate levels in women supplemented with low dose folic acid (up to 1 mg a day) did not correlate with human milk folate level [26,27].

Our findings on the effect of high dose folic acid on asthma medication are in line with evidence from cohort studies on the regular dose of folic acid (0.5 mg) [7-9].

These adverse effects of folic acid are thought to be caused by epigenetic modification [14]. The process of DNA methylation plays a major role in the prenatal development in general [28] and in particular in the early development of the immune system [29,30], therefore the level of folic acid that the child is exposed to prenatally could well affect the early development of asthma. Maternal intake of folic acid determines serum levels of folic acid and is associated with the level of DNA methylation in offspring [13,31]. Our findings may reflect one of the unknown effects of prenatal folic acid exposure by DNA methylation on future health of the children [6].

In our study the reference group consisted of mothers who used no folic acid supplementation or used the regular dose of 0.5 mg. The regular dose of folic acid supplementation is available over the counter and is not registered in the IADB.nl. A recent study about the use of periconceptional folic acid in the Northern Netherlands showed that 85% of women used a folic acid supplementation at any time during the recommended period of 4 weeks before until 8 weeks after conception [32]. We can assume that the majority of the mothers in our reference group took a folic acid supplement during pregnancy. The observed increased risks therefore show the additional risk of high dose folic acid supplementation, not the effect of the regular dose of folic acid supplementation. The impact of dietary folic acid intake will be marginal, because the mean intake in the Netherlands is less than 0.2 mg per day [33].

High dose folic acid has shown to prevent recurrent NTDs [34] and is possibly beneficially for women with low blood folate levels due to a current disease or medication use [35], but currently only little is known about the adverse effects on long term childhood health [6]. This drug dispensing database study suggests that high dose folic acid use during pregnancy increases the risk of childhood asthma. Additional research based on other data sources is recommended to confirm the association found.

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Chapter 3.3 The use of folic acid antagonists during the first trimester of pregnancy, taken with or without folic acid, and their association with folic acid sensitive birth defects.

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Abstract

Objective

To evaluate the association of folic acid (FA) antagonists and the development of FA sensitive birth defects and the effect of FA on this association.

Methods

For this case-control study we used the Eurocat NNL database. Cases were all children/fetuses having FA sensitive birth defects. Controls were all births with a chromosomal or genetic disorder and no birth defect that could also be FA sensitive. When numbers allowed, the effects of two subgroups of FA antagonists, antiepileptic drugs and dihydrofolate reductase inhibitors on the different FA sensitive births defects were investigated separately.

Results

We Identified 2259 cases and 3153 controls. An increased OR was only found for first trimester use of antiepileptic drugs and the occurrence of NTDs (OR: 3.76, 95%CI: 1.09-12.98).

Conclusion

We were able to confirm the established association between first trimester use of antiepileptic drugs and NTDs but other associations found in literature as well as any protective effect of concurrent FA supplementation could not be confirmed. In general, numbers were too low to calculate ORs or to draw conclusions.

Introduction

Folate, a water-soluble B-vitamin has an important role in DNA synthesis and cell proliferation and is therefore critical for fetal development. The increased demand of folate during pregnancy must be met by dietary intake and folate is present as polyglutamate in several foods.

Folate is available as a supplement in its synthetic form, folic acid (FA). FA supplementation has shown to reduce the risk of having a child with a neural tube defect (NTD). A protective effect on other defects like cardiovascular anomalies, urinary tract anomalies, oral clefts, limb reduction defects, omphalocele and anal atresia has also been suggested [1,2].

To meet the recommended amount of folate during pregnancy of 600 mcg per day, several countries like the United Stated fortify grain products with FA. In the Netherlands pregnant women are advised to take a supplement of 400 mcg FA a day, from at least 4 weeks before conception until 8 weeks after.

After consumption, folate is metabolized by dihydrofolate reductase (DHFR) to its bioactive form 5-methyltetrahydrofolate (5-MTHF). 5-MTHF is the main form of folate in the blood circulation and is transported in the cells where it acts as a methyl-acceptor or -donor in important biochemical reactions like pyrimidine synthesis and DNA methylation [3]. This folate metabolism can be disturbed by several drugs (Table 1). Two groups of FA antagonists can be distinguished. One group consists of the DHFR inhibitors and includes methotrexate, sulfasalazine and trimethoprim. The second group contains the drugs that intervene with other reactions of folate metabolism, by antagonizing other enzymes, impairing absorprion or increasing degradation. This group mainly contains antiepileptic drugs, like valproic acid and carbamazepine [1,3].

To evaluate the effects of FA antagonists on the development of FA sensitive birth defects, the Eurocat NNL database can be used. We conducted a case-control study to investigate any increased risk on the development of FA sensitive birth defects after first trimester exposure to FA antagonists. Sub-analyses were performed to determine whether the concomitant intake of FA affects the development of these birth defects.

Methods

For this case-control study we used the EUROCAT NNL database, a population-based birth defects registry in the Northern Netherlands, covering approximately 10% of all births in the Netherlands. Cases are provided by health care workers and hospitals in the region or actively collected by searching hospital files and include live-births, stillbirths, miscarriages and termination of pregnancies. Registration takes place after consent of the parents; the response rate is approximately 80%. Malformations are coded from medical files using the International Classification of Diseases (ICD9/ICD10). Socio-demographic characteristics, details of pregnancy, prenatal screening methods and diagnostic tests, and exposure to possible risk factors are asked to the parents by a mailed questionnaire. Information about dispensed medications three months before and during pregnancy is obtained from pharmacy records after maternal permission. Actual use of the prescribed or any over-the-counter medication is verified in a telephone interview.

All fetuses and children in the database from 1997-2011 with complete data on prescription drugs were selected. Cases are all children/fetuses having FA sensitive birth defects, including NTDs, orofacial clefts, heart anomalies, limb reduction defects, omphaloceles, anal atresias and urinary tract anomalies. When numbers allowed, the effect of FA antagonists on the several births defects were investigated separately. Controls are all births with a chromosomal or genetic disorder. Births with a FA sensitive birth defect together with other congenital malformations, being part of a chromosomal or genetic disorder or any other syndrome, were not defined as cases neither as controls.

A birth was considered to be exposed when a FA antagonist is reported to be used anywhere during the first trimester of pregnancy (the first 13 weeks after the last menstrual period). Subanalyses were made for exposure to antiepileptic drugs and exposure to DHFR inhibitors. For the entire group of FA antagonists and both subgroups, exposure to FA was also evaluated. Exposure to FA was defined as the reported use of FA (at least 400 mcg a day) somewhere in the recommended period from 4 weeks before until 8 weeks after conception. Table 1 shows the FA antagonists that were identified and investigated.

Maternal characteristics that were compared between cases and controls were age of the mother when giving birth, BMI, educational level, smoking, use of alcohol and folic acid use. A T-test was used for continuous variables and a Chi square for categorical variables.

Odds Ratios (ORs) and 95% confidence intervals (CIs) were calculated for all FA sensitive malformations and cases/controls and exposure to FA antagonist, and for exposure to antiepileptics, DHFR inhibitors and other FA antagonists. ORs and 95%CIs were also calculated for cases/control and exposure to one of these groups together or without exposure to FA.

Table 1: Folic acid antagonist identified in literature [3].

ATC code	name	ATC code	name
	antiepileptics		**DHFR-inhibitors**
N03AA02	phenobarbital	A07EC01	sulfasalazine
N03AA03	primidone	C03DB02	triamterene
N03AB02	phenytoin	C03EA01	hydrochlorothiazide + amiloride
N03AF01	carbamazepine	C03EA03	epitizide + triamterene
N03AG01	valproic acid	J01EA01	trimethoprim
N03AX09	lamotrigine	J01EE01	trimethoprim + sulfonamide
		L04AX03	methotrexate
	other	N03AX09	lamotrigine
A10BA02	metformin	P01BD01	pyrimethamine
A10BD02	oral antidiabetic combinations		
C10AC01	colestyramine		
C10AD02	nicotinic acid		
L04AD01	ciclosporin		

Results

Within Eurocat NNL, 7839 children were registered with a date of birth from 1997-2011. In 5912 (74.2%) of these births prescription data were available. We Identified 2259 cases with any of the FA sensitive birth defects defined, including 150 cases with a NTD, 397 with a cleft, 1209 cases with a heart defect, 460 cases with an urinary tract defect , 83 cases with a limb reduction defect, 27 cases with omphalocele, 52 cases with an anorectal defect and 3153 controls.

In total, 73 births (1.3%) were exposed to an FA antagonist during the first trimester of pregnancy. For the mothers of the cases identified, the mean age when giving birth was 30.4 years, which is significantly lower ($p=0.003$) than the mean age of the mothers of our controls (30.8). The mean BMI of the mothers of cases (24.5) was significantly higher ($p<0.001$) than the mean BMI of the mothers of controls (24.0). There was no difference in education, smoking, alcohol use or periconceptional use of folic acid between cases and controls.

Table 2 shows the number of controls and cases exposed to FA antagonist and both subgroups of antiepileptics and DFHR-inhibitors, with calculated ORs and 95%CIs. ORs calculated for associations with less than 3 cases exposed to the exposure investigated are considered to be less accurate due to low numbers and will not be taken into account when considering possible risks. For reduction defects, omphaloceles and anorectal defects we had no cases in our dataset, for these malformation groups no ORs could be calculated.

Table 2: Numbers of controls and cases exposed with Odds Ratios and 95% Confidence Intervals.

	controls (n=3153)	all FA-sensitive defects (n=2259)	
	n	n	OR (95%CI)
Exposure			
no exposure	3111	2228	reference
exposed to all FA-inhibitors	42	31	1.03 (0.65-1.64)
exposed to antiepileptics	17	11	0.90 (0.42-1.93)
exposed to DHFR inhibitors	23	14	0.85 (0.44-1.66)
other FA-inhibitors	5	5	1.40 (0.40-4.83)
Exposure with or without the use of FA			
no exposure and **no** FA use	800	609	reference
no exposure and FA use	2258	1583	0.92 (0.81-1.04)
exposed to all FA-inhibitors and FA use	33	24	0.95 (0.56-1.63)
exposed to all FA-inhibitors and **no** FA use	9	5	0.73 (0.24-2.18)
Exposure	controls (n=3153)	NTDs (n=150)	
no exposure	3111	146	reference
exposed to all FA-inhibitors	42	4	2.03 (0.72-5.74)
exposed to antiepileptics	17	3	***3.76 (1.09-13.00)***
exposed to DHFR inhibitors	23	1	0.93 (0.12-6.91)
other FA-inhibitors	5	0	
Exposure with or without the use of FA			
no exposure and **no** FA use	800	48	reference
no exposure and FA use	2258	100	0.74 (0.52-1.05)
exposed to all FA-inhibitors and FA use	33	5	2.50 (0.94-6.78)
exposed to all FA-inhibitors and **no** FA use	9	0	
Exposure	controls (n=3153)	clefts (n=397)	
no exposure	3111	391	reference
exposed to all FA-inhibitors	42	6	1.14 (0.48-2.69)
exposed to antiepileptics	17	0	
exposed to DHFR inhibitors	23	4	1.38 (0.48-4.02)
other FA-inhibitors	5	2	1.59 (0.19-13.66)
Exposure with or without the use of FA			
no exposure and **no** FA use	800	101	reference
no exposure and FA use	2258	291	1.02 (0.80-1.30)
exposed to all FA-inhibitors and FA use	33	5	1.20 (0.46-3.14)
exposed to all FA-inhibitors and **no** FA use	9	0	
Exposure	controls (n=3153)	heart defects (n=1209)	
no exposure	3111	1193	reference
exposed to all FA-inhibitors	42	16	0.99 (0.56-1.77)
exposed to antiepileptics	17	7	1.07 (0.44-2.60
exposed to DHFR inhibitors	23	7	0.79 (0.34-1.85)
other FA-inhibitors	5	2	1.04 (0.20-5.38)
Exposure with or without the use of FA			
no exposure and **no** FA use	800	328	reference
no exposure and FA use	2258	831	0.90 (0.77-1.04)
exposed to all FA-inhibitors and FA use	33	12	0.89 (0.45-1.74)
exposed to all FA-inhibitors and **no** FA use	9	3	0.81 (0.22-3.02)

Table 2 – continuation.

	controls (n=3153)	urinary tract defects (n=460)	
Exposure	n	n	OR (95%CI)
no exposure	3111	454	reference
exposed to all FA-inhibitors	42	6	0.98 (0.41-2.32)
exposed to antiepileptics	17	1	0.40 (0.05-3.04)
exposed to DHFR inhibitors	23	3	0.89 (0.27-2.99)
other FA-inhibitors	5	2	2.74 (0.53-14.17)
Exposure with or without the use of FA			
no exposure and **no** FA use	800	122	reference
no exposure and FA use	2258	326	0.95 (0.76-1.19)
exposed to all FA-inhibitors and FA use	33	4	0.79 (0.27-2.36)
exposed to all FA-inhibitors and **no** FA use	9	2	1.44 (0.31-6.75)

Discussion

In this case-control study into the development of FA sensitive birth defects after first trimester exposure to FA antagonists we did not find an increased OR for folic acid sensitive birth defects after first trimester use of a FA antagonist. Investigating the subgroups of FA sensitive births defects, an increased OR was only found for first trimester use of antiepileptic drugs and the occurrence of NTDs (OR: 3.76, 95%CI: 1.09-12.98).

The association between maternal use of antiepileptic drugs, especially valproic acid, and the occurrence of NTDs [4-6] as well as the association between FA and the prevention of NTDs [8,9] are well established. The potential of FA to prevent NTDs with maternal first trimester use of antiepileptic drugs is still to be clarified since scientific literature is inconclusive [1,10,11]. We had no NTD-cases exposed to antiepileptic drugs during the first trimester of pregnancy without FA supplementation anywhere during the recommended period, therefore we could not investigate the preventive effect of FA for women using antiepileptic drugs.

Associations between first trimester use of antiepileptic drugs and oral clefts, heart defects or urinary tract defects have also been reported in literature [1,12,13]. In our study we did not find an increased OR for heart defects after first trimester use of antiepileptic drugs (OR: 1.07, 95%CI: 0.44-2.60). For oral clefts we had no exposed cases and for urinary tract defects we only had one case exposed to antiepileptic drugs.

In their research at FA antagonists and the risk of birth defects, Hernández-Díaz et al found an increased risk for heart defects and oral clefts after first trimester use of DHFR inhibitors [1]. Associations between maternal use of trimethoprim (in combination with sulfonamides), by far the most commonly used DHFR inhibitor, with NTDs, heart defects or multiple birth defects have also been identified [14,15]. We did not find an increased risk for the development of any FA sensitive birth defects after first trimester use of DHFR inhibitors (OR: 0.85, 95%CI: 0.44-1.66), nor for oral clefts (OR: 1.38, 95%CI: 0.48-4.02), heart defects (OR: 0.79, 95%CI: 0.34-1.85) or urinary tract defects (OR: 0.89, 95%CI: 0.27-2.99). For NTDs, we only had one case exposed. We did not find an association between DHFR inhibitors and any of the malformation groups while taking exposure in the three months before pregnancy together with exposure in the first trimester (data not shown). In the Netherlands trimethoprim with or without sulfonamides is usually only prescribed for 3-5 days. This period might be too short to cause low blood folate levels endangering organogenesis of the fetus.

The OR for the risk of NTDs after the use of FA supplement anywhere during the recommended period was 0.74, for heart defects the OR was 0.90, both nearly reaching significance (upper limit 95%CI respectively 1.05 and 1.04). These values are in line with the established protective effect of FA on the development of NTDs and heart defects [8,9,16].

Women who had taken FA only during part of the recommended period might still have had low folate levels during organogenesis, diluting the protective effect of taking FA supplementation.

Investigating the protective effect of FA for women taking FA supplementation during the entire recommended period compared to women not taking any FA during pregnancy at all gave similar results (data not shown). This might indicate that folate levels during the first weeks of pregnancy of women reporting FA supplementation during part of the recommended period and women reporting FA supplementation during the entire recommended period did not differ substantially.

It is suggested that the concurrent intake of folic acid while using a FA antagonist can lower possible risks of other folate sensitive congenital malformations as well [14,15]. In our study we did not find a significant protective effect of the use of FA supplementation when using a FA antagonist during the first trimester of pregnancy.

Malformed controls are often point of discussion in case-control studies. It is never completely sure that the exposure under study has no effect on the outcome. By taking chromosomal and genetic disorders as controls, that have their origin before development of the fetus and excluding all births with an accompanying defect that could also be FA sensitive, the chances of misclassification are very low. And by using malformed controls recall bias is avoided.

Age of the mother effects the occurrence of congenital malformations. Especially chromosomal defects are more common in children carried by older women. This explains the older age of the mothers in our control group. Congenital malformations are more common in obese women, explaining the difference in mean BMI between mothers of cases and controls. Because of the low numbers in many of the case groups studied, we did not control for possibly confounding factors.

For risk assessment studies looking at birth defects, and especially birth defects that are rare, acquiring an adequate number of cases is a challenge. For many of the associations studied numbers were too low to calculate ORs or to draw conclusions. Yet, our study does not support the hypothesis that the use of FA antagonists in general before and during the first weeks of pregnancy is a risk factor for the development of FA sensitive birth defects. We were able to confirm the established association between first trimester use of antiepileptic drugs and NTDs but other associations found in literature as well as any protective effect of concurrent FA supplementation could not be confirmed. We recommend to investigate the relation between FA antagonists and FA sensitive birth defects and the possible effect of additional FA in other large databases with data on birth defects and medication use.

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Chapter 3.4 Identifying Associations between Maternal Medication Use and Birth Defects Using a Case-Population Approach: An Exploratory Study on Signal Detection.

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Abstract

Background

The effects of many drugs on the unborn child are unknown. In a case-population design, drug exposure of cases is compared to that of a source population. This kind of study can be useful for generating signals.

Objective

To see whether a comparison of drug use rates from the birth defect registry EUROCAT NNL (cases) with prescription rates from a population-based prescription database, the IADB.nl, (population), could be used to detect signals of teratogenic risk of drugs.

Methods:

We defined 3212 cases from the EUROCAT NNL database, a population-based birth defect registry in the Northern Netherlands and 29,223 population controls from the IADB.nl, a prescription database with data from community pharmacies in the same geographical area, born between 1998 and 2008. We classified the malformations of the 3212 cases into several malformation groups according to organ system (based on the ICD codes and the EUROCATguidelines). If a child had multiple malformations in several organ systems (n=253, 7.9%), it was counted in all the categories represented. For several groups of malformations we calculated rate ratios (RR) and 95% confidence intervals (CI) for drugs acting on the nervous system and drugs considered to be safe for use in pregnancy. The RRs were based on first trimester drug utilization rates from the cases in the EUROCAT NNL database and prescription rates from the population controls in the IADB.nl.

Results

For drugs acting on the nervous system we found significantly increased RRs for the antiepileptic drug valproic acid and for some SSRIs. Of drugs considered to be safe, only the antihypertensive methyldopa showed significantly increased RRs.

Conclusion

We show that a case-population study is a suitable method for detecting signals of possible teratogenicity, provided that the teratogenic effects and drugs under study are as specific as possible and the drugs are widely used.

Background

The first trimester of pregnancy is the critical period for the developing embryo, since the organogenesis takes place during these first weeks [1]. Many pregnant women use at least one drug on prescription during this first trimester with estimations varying between 22-54% [1-4]. However, for many drugs on the market, the effects on the unborn child still have to be established. Since results from animal studies do not always predict teratogenicity in humans and pregnant women are excluded from pre-marketing trials for ethical reasons, post-marketing surveillance is necessary [5-7].

When a drug enters the market, it takes some time before enough pregnant women are exposed to it and a proper cohort or case-control study can be performed. At first, mainly case reports or case series will be found in the literature. Several pharmacoepidemiological approaches have been established for rapidly identifying any adverse drug effects, like the case-population and case-cohort designs [8-11]. The case-population or population-based case-cohort approach compares past exposure to a given risk factor in subjects presenting a given disease or symptom (cases) with the exposure rate to this factor in the source population or in the whole cohort [11]. This design can detect rare but serious adverse drug reactions not discovered by clinical trials and has predominantly been used in post-marketing surveillance of adverse drug effects [8-11]. Conditional on having a representative source population, case-population studies are relatively rapid and inexpensive. For the estimation of exposure to the drug under study in the population the cases come from, general consumption data are used [10]. The main limitation of this approach is that general consumption data are often not available.

In this study we explored whether a case-population design can be used to detect signals of teratogenicity as well, by comparing cases from a population-based birth defect registry, with controls derived from a population-based prescription database.

Methods

Cases

Cases were selected from EUROCAT NNL, a population-based birth defect registry in the northern part of the Netherlands, covering approximately 10% of all births in the country. A child can be registered in the database up to the age of 16, there is no lower age limit. All types of births are included in the registry: live births, stillbirths, spontaneous abortions and terminations of pregnancy [12].

Parental informed consent is required for registration. Approximately 80% of the parents agree with inclusion of their child in the registry. Parents are asked to complete a questionnaire with questions about socio-demographic characteristics, prenatal screening methods and diagnostic tests, and exposure to possible risk factors (chemicals, recreational drugs, etc.). Maternal permission is asked to obtain the mother's pharmacy records for the period of 3 months before conception until delivery. Actual use of the prescribed medication is verified in a telephone interview and only the actually used medication is registered [12]. Information on congenital malformations is obtained from the medical files, including pathology reports, and coded afterwards, according to the International Statistical Classification of Diseases and Related Health Problems (ICD) coding system (until 2001: ICD-9; from 2002: ICD-10) by trained registry staff. Drugs that were taken by the mother are coded according to the Anatomical Therapeutic Chemical (ATC) classification system [1, 13, 14].

From the EUROCAT NNL database we selected all fetuses and children (live births, stillbirths, spontaneous abortions and terminations of pregnancy) born between 1998 and 2008 (n=6025). We excluded cases without complete pharmacy records and without complete information regarding medication use (n=1606; 26.7%). Since genetic and chromosomal disorders are not thought to be related to maternal medication use [15], cases with a genetic or chromosomal disorder (n=1207; 20.0%) were also excluded. Our final dataset consisted of 3212 cases. The cases were classified into different groups of malformations based on the ICD codes and the EUROCAT guidelines [16]. Table 1 shows the number of cases classified into the different malformation groups. Appendix 2 gives a list of all the malformations that are coded within the different malformation groups studied. If a child had multiple malformations, it was counted in all the categories represented (n=253, 7.9%), therefore numbers do not add up to 3212. However, a child with several different cardiac malformations is only counted as one case within the groups of heart defects.

Table 1: Number of cases classified into the different malformation groups compared to the percentage of children born within these groups in the total population.

Malformation group	Cases n (% of 3212)
Malformations of the central nervous system	208 (6.4)
Cardiac malformations	873 (27.2)
Clefts	294 (9.2)
Malformations of the respiratory tract	55 (1.7)
Malformations of the digestive system	362 (11.2)
Genital malformations	314 (9.8)
Malformations of the urinary tract	309 (9.6)
Malformations of the musculo-skeletal system	668 (20.8)
Malformations of the limbs	184 (5.7%)

Population

From the IADB.nl, a population-based prescription database, which contains prescription data from approximately 55 community pharmacies in the Netherlands we selected the population controls. The IADB.nl covers an estimated population of 500,000 individuals, which is considered representative of the general population. Because most Dutch patients only use one pharmacy, an almost complete medication history of each individual is registered in the database. Prescribed drugs are recorded by their ATC code [14]. Data on date of dispensing, amount dispensed, dose regimen and the prescriber are also available. Each patient has a unique, anonymous identifier and their date of birth and gender are known. No information about medication prescribed during hospitalization or over-the-counter (OTC) drugs is available.

For the IADB.nl pregnancy database, pregnancies are identified by connecting a child in the IADB.nl to the female aged 15-50 years with the same address code as the child, providing there were no other females of this age with the same address code. This method allows 64.9% of the mothers to be identified. Validation of this method has been described elsewhere [17]. The theoretical pregnancy period is defined by taking the date of birth of the child minus 273 days (3 trimesters of 91 days). All 29,223 children, born from 28,528 pregnancies, with a date of birth between 1998 and 2008 were included in this study, including 1320 twins and 56 multiple births.

Drugs

Because malformations develop in the first trimester of pregnancy, [1] we focused on drug use and prescription during this period. We defined the first trimester as the first 13 weeks of pregnancy. A case was defined to be exposed to one of the drugs under study when the drug was registered to be used during the first 13 weeks after the first day of the last menstrual period (LMP). For the population the exposure definition was based on the date of prescription: if the mother received a prescription in the first 13 weeks of pregnancy, the child was considered exposed.

We selected two drug groups for our case-population study. The first group consisted of all drugs acting on the nervous system (drugs with an ATC code starting with N). These types of drugs have been studied frequently and certain teratogenic effects have been identified, especially with the antiepileptics [5, 18-24]. A suitable method to detect signals of teratology should be able to detect known teratogenic effects. The second group consisted of all drugs considered to be safe, classified as A ("drugs that have been taken by a large number of pregnant women and women of child-bearing age without an increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed") according to the Australian Drug Evaluation Committee (ADEC) [25],

except drugs for fertility treatment. We did not expect any teratogenic effects to be found in this group.

The ATC classification is based on the organ system that a drug acts on and subsequently on its therapeutic and chemical characteristics, while the ADEC classification aims to classify risks associated with taking particular medicines in pregnancy based on the available evidence [13,25]. The two drug groups under investigation were therefore composed differently. Because the IADB.nl does not contain information on the use of OTC medication, only prescribed drugs were included.

Analyses

For the cases and population, mean maternal age and the distribution of the birth years over the study period were calculated and compared using the t-test and the Mann Whitney U test, respectively.

From the EUROCAT NNL data, we calculated first trimester user rates among malformation groups as the percentage of cases exposed to a specific drug. To reduce the risk of chance findings, we calculated user rates only for drug groups and for specific drugs with at least three exposed cases in the first trimester. From the IADB.nl data, we calculated prescription rates as the percentage of infants exposed in utero.

Because a drug usually acts on a certain organ system and causes specific birth defects, we did not compare the user rate among all malformations together with the IADB.nl prescription rates. By taking all malformations together, any teratogenic effect would have been diluted and signals could have been missed.

The drug use rates among the malformation groups were compared with the IADB.nl prescription rates by calculating rate ratios (RR) and 95% confidence intervals (CI). Analyses were performed using PASW Statistics (IBM, Chicago, IL, USA, Version 18).

Results

Table 2 shows the distribution of the birth years of the cases and our population per study year. The number of births per year decreased over time for the population, because it can take some time before a pregnancy is identified in the IADB.nl.

Table 2. Distribution of the birth years of the cases (EUROCAT NNL) and general population (IADB.nl) per study year.

	EUROCAT NNL (n-tot=3212)		IADB.nl (n-tot=29223)	
Study year	n	%	n	%
1998	294	9.2	3136	10.7
1999	303	9.4	3353	11.5
2000	286	8.9	3256	11.1
2001	273	8.5	3105	10.6
2002	280	8.7	3043	10.4
2003	320	10.0	2887	9.9
2004	307	9.6	2763	9.5
2005	305	9.5	2419	8.3
2006	316	9.8	2006	6.9
2007	260	8.1	1740	6.0
2008	268	8.3	1515	5.2

Table 3. User rates (cases) and prescription rates (general population) for the drugs investigated.

	CASES - malformation categories [1] (n=3212)									POPULATION (n=29223)
	CNS (n=208)	*heart (n=873)*	*clefts (n=294)*	*respiratory tract (n=55)*	*digestive system (n=362)*	*genitals (n=314)*	*urinary tract (n=309)*	*muscular-skeletal (n=668)*	*limbs (n=184)*	
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Drugs acting on nervous system (ATC code: N)										
sumatriptan	0	4 (0.46)	0	0	0	0	<3[2]	0	0	58 (0.20)
valproic acid	3 (0.01)	5 (0.57)	<3[2]	0	<3[2]	0	<3[2]	<3[2]	0	28 (0.09)
diazepam	<3[2]	3 (0.34)	<3[2]	<3[2]	0	<3[2]	<3[2]	<3[2]	<3[2]	86 (0.29)
oxazepam	<3[2]	3 (0.34)	<3[2]	<3[2]	3 (0.96)	<3[2]	<3[2]	3 (0.45)	0	161 (0.55)
fluoxetine	<3[2]	3 (0.34)	<3[2]	0	3 (0.96)	0	0	<3[2]	0	65 (0.22)
citalopram	0	0	0	0	<3[2]	0	0	3 (0.45)	0	35 (0.12)
paroxetine	0	11 (1.26)	<3[1]	0	<3[2]	<3[2]	4 (1.29)	4 (0.60)	0	181 (0.62)
Drugs considered to be safe (ADEC classification: A)										
metoclopramide	<3[2]	5 (0.57)	<3[2]	0	<3[2]	<3[2]	<3[2]	<3[2]	<3[2]	155 (0.53)
methyldopa	0	0	0	0	3 (0.83)	3 (0.96)	3 (0.97)	<3[2]	0	52 (0.18)
thyroxine	<3[2]	10 (1.15)	3 (1.02)	0	4 (1.10)	<3[2]	<3[2]	6 (0.90)	3 (1.63)	299 (1.02)
amoxicillin	11 (5.29)	28 (3.21)	13 (4.42)	4 (7.27)	19 (5.25)	14 (4.46)	13 (4.21)	21 (3.14)	7 (3.80)	994 (3.40)
nitrofurantoin	<3[2]	10 (1.15)	3 (1.02)	<3[2]	3 (0.83)	<3[2]	4 (1.29)	9 (1.35)	3 (1.63)	388 (1.33)
salbutamol	5 (2.40)	8 (0.92)	3 (1.02)	<3[2]	7 (1.93)	8 (2.55)	6 (1.94)	13 (1.95)	5 (2.72)	426 (1.46)
budesonide	0	5 (0.57)	<3[2]	<3[2]	<3[2]	<3[2]	<3[2]	<3[2]	<3[2]	83 (0.28)

ATC = Anatomical Therapeutic Chemical; ADEC = Australian Drug Evaluation Committee

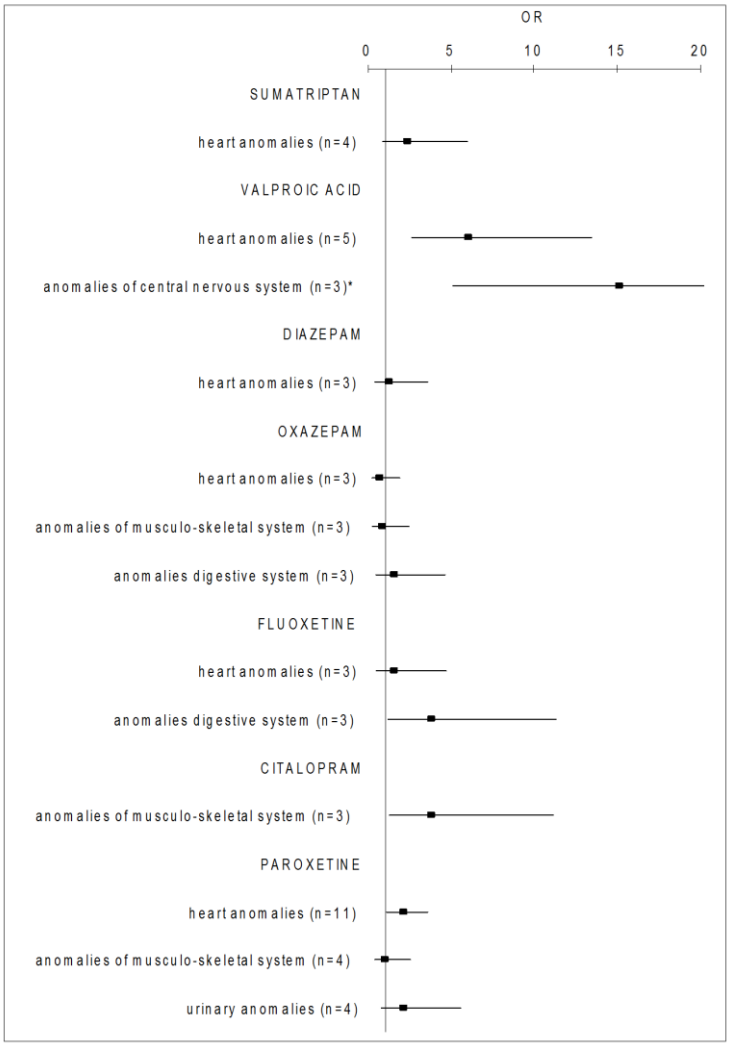
[1] children with multiple malformations were counted in multiple categories (n=253, 7.9%)

[2] unequal to 0, but numbers too low to calculate a reliable RR

A Mann Whitney U test showed no significant difference (p=0.412) between the distribution of the years of birth of the cases and of the IADB.nl population in the study period. The mean age of the case mothers at birth was 30.4 years. The mean age of the population mothers at birth was 30.0 years. A t-test showed a significant difference ($p < 0.001$).

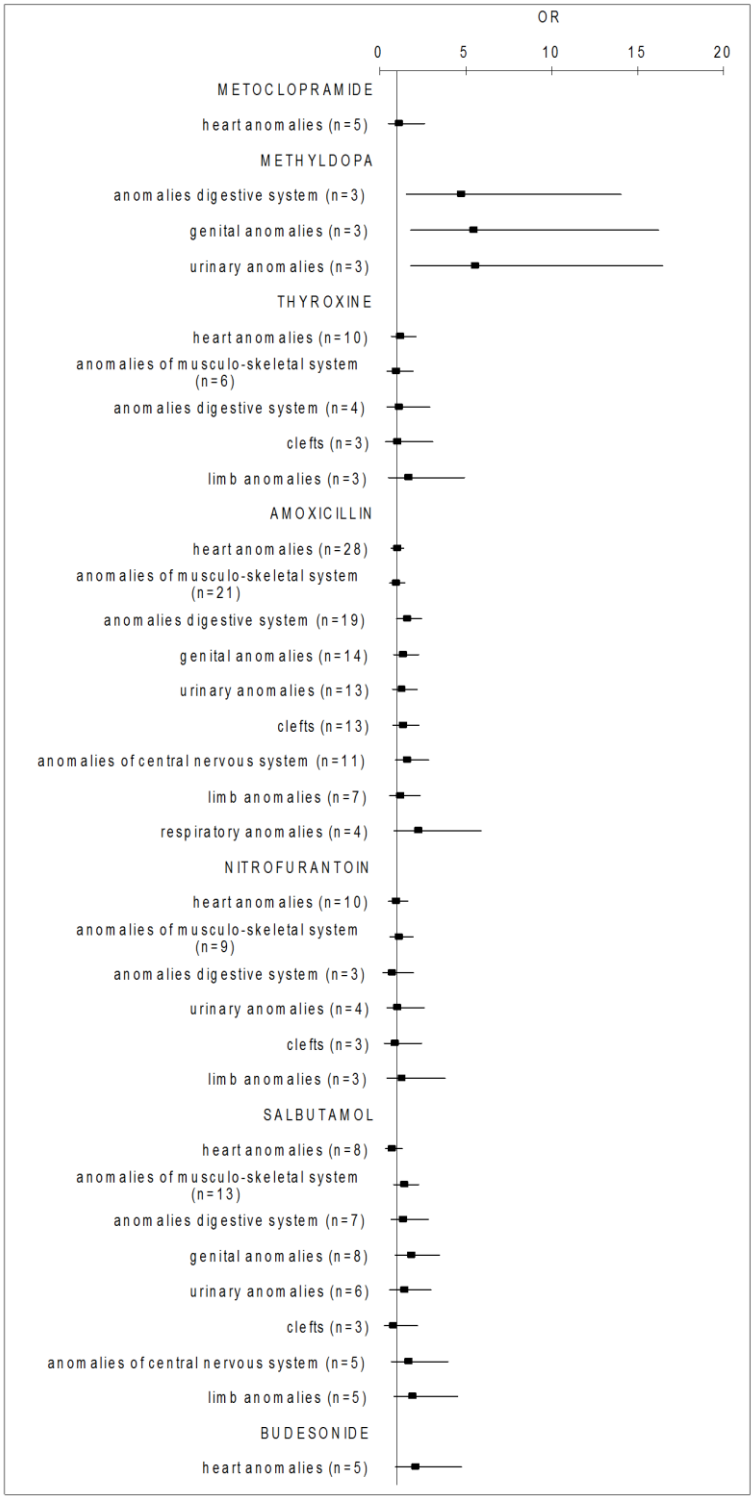
Table 3 shows the user rates (cases) and prescription rates (population) for the drugs investigated according to malformation group. Based on our criterion of at least three exposed cases, seven specific drugs acting on the nervous system and seven specific drugs considered to be safe were included in our analyses.

Figure 1. Rate ratios (RR) calculated for drugs acting on the nervous system for the different malformation groups.



* Valproic acid – anomalies of central nervous system (n=3) 15.05 (5.09-44.51)

Figure 2. Rate ratios (RR) calculated for drugs considered to be safe for the different malformation groups.



Drugs acting on the nervous system

Figure 1 shows the RRs for the drugs acting on the nervous system that could be calculated for the malformation groups. The antiepileptic drug valproic acid showed a significantly increased RR for heart anomalies of 5.98 (2.66-13.44) and for anomalies of the central nervous system of 15.05 (5.09-44.51). For some selective serotonin reuptake inhibitors (SSRIs), we found certain significantly increased RRs: fluoxetine and anomalies of the digestive system: 3.73 (1.23-11.32); citalopram and anomalies of the musculo-skeletal system: 3.75 (1.26-11.14) and paroxetine and heart anomalies: 2.03 (1.14-3.62). The malformations observed can be found in Appendix 3. We found no significantly increased RR for the anti-migraine drug sumatriptan, nor for the benzodiazepines, diazepam and oxazepam.

Drugs considered to be safe

The RRs for specific drugs in the group of 'safe' drugs are shown in Figure 2. The antihypertensive methyldopa showed significantly increased RRs for anomalies of the digestive system : 4.66 (1.54-14.06) genital anomalies: 5.37 (1.78-16.22) and urinary anomalies: 5.46 (1.81-16.49). We found no significantly increased RR for metoclopramide, thyroxine, amoxicillin, nitrofurantoin, salbutamol or budesonide.

Discussion

In this case-population study, we investigated whether comparing drug use rates from a population-based birth defects registry with prescription rates from a population-based prescription database could be used as a suitable detection method for the teratogenic risk of drugs. For drugs acting on the nervous system, we found significantly increased RRs for the antiepileptic drug valproic acid and for some SSRIs. Of the drugs considered to be safe, only the antihypertensive methyldopa showed significantly increased RRs.

A suitable method for the detection of possible teratogenicity should be able to detect known teratogenic effects but should not detect any effects if a drug is considered to be safe. Based on the Bradford Hill criteria on causality [26], Meyboom et al. stated seven basic criteria for determining a signal [27,28]. Of these criteria "quantitative strength of the association, consistency of the data, biological plausibility and experimental findings" can be applied to our study. A method to detect signals must pick up signals quickly and easily, and should therefore be easily applicable and relatively inexpensive. Although they have limitations, like needing to control for potential confounders and quantifying the strength of the association found, case-population studies are considered to be useful for generating signals and testing hypotheses [11].

For the antiepileptic drug valproic acid we found increased RRs for heart anomalies and for anomalies of the central nervous system. These results are in line with previous results [18,19,21,22,29]. The association between fluoxetine and anomalies of the digestive system was previously reported by Bakker et al. [30] using the same data from EUROCAT NNL. This association was confirmed by Colvin et al [31].

Citalopram has been associated in the literature with neural tube defects [32] and septal heart defects [33] but we found no report of an association with musculo-skeletal malformations. The association we found was based on three cases: two of them were affected by singular dysplasia of the hip, while the third case had a dysplasia and luxation of the hip. The broad confidence interval around the RR of 3.75 (1.26-11.14) indicates that this estimate is not very precise.

As far as we know, this is the first report of such an association. There is no evidence of biological plausibility for the association of citalopram with hip anomalies. It should be noted that hip malformations are common in the Northern Netherlands, with an etiology that showed to be multifactorial [34] and is unlikely to be drug-induced. Our finding therefore needs further investigation in other datasets.

We found an increased RR for paroxetine and heart anomalies in general. The association between paroxetine and cardiac malformations, especially right ventricle outflow tract obstructions, has been reported by several other studies [33,35,36]. Using data from the same birth defect registry, EUROCAT NNL, a recent case-control study on first trimester use of paroxetine and congenital heart defects found a significantly increased risk for atrium septum defects but not for heart anomalies in general [37]. The association between paroxetine and cardiovascular malformation is still point of discussion though. In his study of three meta-analyses on this topic, Scialli states that by applying the Bradford Hill criteria of causality noted before, 'scientific evidence does not support for the conclusion that paroxetine causes cardiovascular defects' [38].

As expected, the RRs we found for the drugs considered to be safe were generally around one. However, significantly increased RRs were found for methyldopa and anomalies of the digestive system, genital anomalies and urinary anomalies. One child contributed to all of these malformation groups. Due to low numbers this had a substantial effect on the RRs calculated possibly leading to a false-positive signal. Furthermore, methyldopa is the most extensively used antihypertensive in pregnancy, because it is considered to be safe and efficient [39].

A number of studies have shown little difference in teratogenic risk between several antihypertensive medications and untreated hypertension, suggesting that the underlying hypertension itself might increase the risk for congenital malformations [40-43]. Additional studies are needed to elaborate on these findings.

Strengths and limitations

Comparing data from EUROCAT NNL and IADB.nl offers the opportunity to compare first trimester drug exposure based on pharmacy data in two different databases, covering approximately the same geographical area and the same period. Since the data are available, the method is relatively easy and inexpensive.

The IADB.nl is a population-based, non-selected database, including a large number of pregnancies [17]. Almost complete records of prescription data are available because Dutch normally only use one local pharmacy. For EUROCAT NNL, information about drug use is based on pharmacy records and verified in telephone interviews. The complementary use of pharmacy records and interview data provides the most complete medication history possible [44].

When using data from a prescription database, it is unknown whether the drug was actually taken, possibly leading to an overestimation of drug use. Olesen et al [45] studied pregnant women's compliance in using prescribed drugs and found that it was high for drugs used to treat chronic diseases (70-100%) but lower for short-term treatments. Another limitation is that since we only focused on the prescription date and not on the duration of the prescription, we will have missed drugs prescribed before the pregnancy, but used during pregnancy. The IADB.nl only contains live births and has no information about congenital malformations, but since it is a population-based record, we expect about 3% of the children to have a congenital anomaly [46]. These low numbers will only cause a minimal bias.

The actual gestational period of the pregnancies in the IADB.nl is not known. Taking the theoretical gestation to determine first trimester exposure may have led to some misclassifications. For more than one third of all children registered with the IADB.nl a mother cannot be identified, possibly leading to selection bias. However criteria for linking a child to a parent are very strict to avoid mismatching. Schirm et al demonstrate that more than 99% of the coupled children were coupled to the right mother [17]. For EUROCAT NNL, approximately 80% of the parents agree with inclusion of their child in the registry. Women who agree with registration might differ from women who do not agree with regard to type of anomaly or demographic factors, therefore selection bias cannot be excluded.

Only cases with complete pharmacy records and medication use were included. The cases excluded from the study population contained more miscarriages, terminated pregnancies and stillbirths than the cases with complete records and were relatively earlier in our study period. Malformations amongst stillbirths and terminations differ from malformations amongst live born, often being more serious and not compatible with life. Medications used might be different for these groups as well. Some bias may have occurred, which could have led to underestimation of medication use among cases and not detecting some signals. However, this selection criterion was necessary to ensure the quality of our data.

We found a significant difference among the mean ages of the case and population mothers. In absolute terms, the difference is only of a small order, i.e. 0.4 years. Ideally, the results should be adjusted for age. However, due to small numbers adjustment was not possible.

Due to the nature of the population data used, we were not able to adjust for potential confounding factors. Since we wanted to test a method for detecting signals quickly and easily, further studies designed to confirm or reject the signals we found should address the issue of confounders.

We could not detect associations described in the literature for several drugs acting on the nervous system. Some of these associations, like the increased risk of clefts with exposure to diazepam, are controversial and literature reports are often inconsistent. We could only calculate RRs for a limited association between drugs and malformations groups because of small case groups and the incidental use of several drugs. Sample size calculations show that for the detection of a small risk (RR=2) and an exposure of 0.2% in the pregnant population, like for some of the medication from the drugs acting on the nervous system we studied, approximately 7100 cases would be needed. For a relatively common birth defect like a heart defect (prevalence 0.7%), this would cover about 1 million births. Larger databases are necessary to detect potential teratogenic effects of drugs not commonly used, from a large registration area with population data and also information on drug use. This could probably be realized by adding other congenital anomaly registries with detailed information about drug use and the availability of population data.

In Conclusion

This study was conducted to test the case-population approach for detecting signals, by comparing exposure rates between cases (from a birth defect register, EUROCAT NNL) and the general population (represented by a pharmacy database, IADB.nl). We show how this method was able to detect known teratogenic risks for several widely used drugs acting on the nervous system. It did not detect any teratogenic effects for most drugs that are considered to be safe, assuming there were enough cases for a particularly anomaly. We can therefore assume that this is a suitable method for detecting signals of possible teratogenicity, providing that the teratogenic effects and drugs studied are as specific as possible, and the drugs are widely used.

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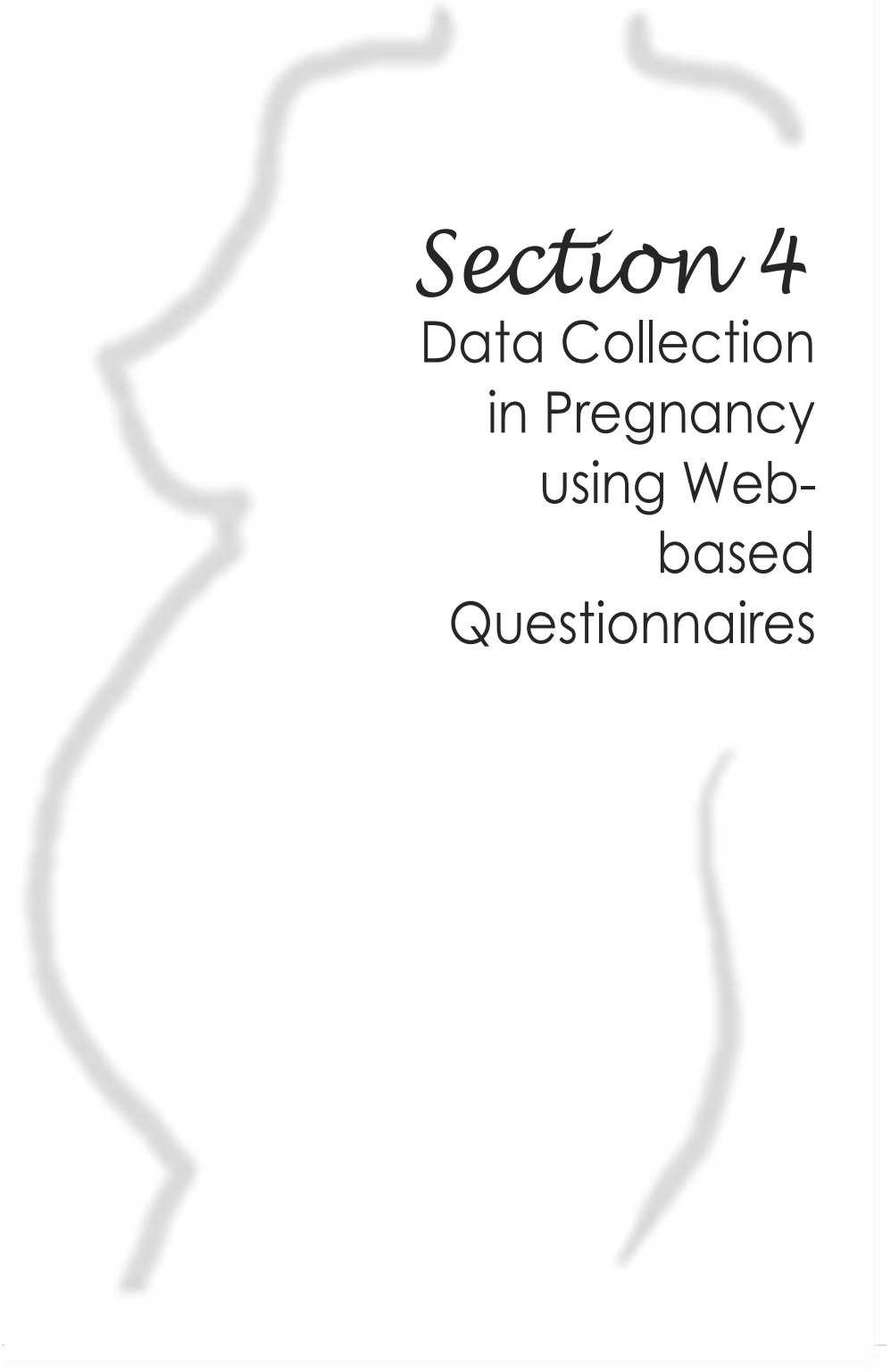

Section 4

Data Collection in Pregnancy using Web-based Questionnaires

Chapter 4.1 The use of Internet surveys in epidemiological research aiming at pregnant women or addressing a topic associated with pregnancy.

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Submitted for publication

Abstract

The use of Internet surveys for epidemiologic research is increasing. With this review we investigate the use of web-based surveys examining a pregnancy-related topic.

The literature search using the PubMed and the EMBASE database resulted in a final sample of 37 eligible publications published from 2000 to 2013. Of all publications found, 25 (67.6%) discussed a health-related topic, 10 (24.3%) discussed a methodological topic and 3 (8.1%) had investigated Internet use. Investigators used different methods for the recruitment of participants and recruitment time and recruited numbers were very different as well. The questionnaires of the studies using the Internet as main recruitment method were accessible from 24 hours until several years and these questionnaires were completed by 88 to 9,483 participants. Generally, participants included in the studies investigated, were older, higher educated and more 'white' than the target population.

We conclude that the Internet can be used for questionnaire based studies to investigate perceptions of pregnant women or topics related to pregnancy assessing associations between variables and outcomes, providing the recruitment method used is efficient and well-targeted. Data obtained via open recruitment on the Internet is less suitable to calculate prevalences.

Introduction

Along the history of epidemiologic surveys, data collection has been performed using several methods, the most common being the face-to-face interview, telephone interview and pen-and-paper questionnaire. The cost-effectiveness of these traditional modes has been a point of discussion. Distributing and collecting questionnaires or performing interviews is time consuming and expensive and recruitment rates are declining over the years, probably because of an increase in the number of surveys posted and the effort asked of survey participants like biological sampling and follow up together with a general decrease of volunteerism [1].

Since the Internet was introduced in the late 1990s, researchers started to investigate its possibilities as a tool for data collection. More people are online every year [2,3] and due to the advantages, the use of Internet surveys for epidemiologic research is increasing subsequently [4]. A web-based survey is convenient for the participants, data collection is more efficient, direct entry of the data in the database assures data quality and many potentially eligible subjects are to be reached [5,6].

There is still some concern though about the validity of data collected and the possibility of selection bias [7,8], but research has shown that respondents attending a web-based survey are comparable to the ones participating in traditional survey methods and information acquired is at least as reliable [5,9]. The current march of the smartphone and tablet entailing permanent access to the Internet and the extensive use of social media create even more possibilities in using the Internet for research purposes.

Epidemiological studies play an important role in the assessment of health, lifestyle choices and medication use during pregnancy. An Italian survey among pregnant women showed that 95% used the Internet and almost all of these women searched the Internet for pregnancy-related issues [10]. These numbers will be comparable for the rest of the Western world. This makes the Internet pre-eminently suitable for reaching pregnant women for epidemiologic surveys.

The aim of this review is to investigate the use of web-based surveys addressing women planning a pregnancy, being pregnant or having given birth. We will evaluate the benefits and drawbacks, the topics covered, and validity and completeness of the web-based surveys compared to traditional methods.

Methods

We performed a literature search using the PubMed and the EMBASE database to identify all relevant articles. Search terms used were: (Internet or web-based) and (questionnaire or survey) and ("pregnant women" or pregnancy). Publications were checked according to the following criteria: studies collecting data, using a questionnaire posted on the Internet; published in 2000 - 2013; written in the English language; addressing pregnant women, women trying to conceive or women who gave birth participating in a study with a topic concerning pregnancy. Publications with different modes of data collection (for example, women could attend by completing a questionnaire on the Internet or by returning a paper questionnaire) were only included when the characteristics and results of both groups were shown separately. If there were multiple publications using data derived from the same questionnaire, the information about the study design was clustered and the publications were listed as one study.

Results

The literature search performed in April 2014 resulted in 507 references using PubMed and 552 references using EMBASE. All titles and abstracts and if necessary the body text were checked using the criteria stated above, resulting in a final sample of 37 eligible publications shown in Tables 1a-1c, sorted by topic. More extensive information about the selected publications can be found in Appendix 5.

Table 1a. Eligible surveys addressing women planning a pregnancy, being pregnant or having given birth, published from 2000 to 2013, investigating a health-related topic.

Refe-rence	Topic	Recruitment	Recruitment period	Response
11	asthma during pregnancy	invitation at homepage of the investigators institution	3 months	300 responses, final sample: 166
12	smoking cessation	links to smoking cessation website	11 months	491 responses, 443 eligible
13	getting pregnant	on a website related to the topic	8 weeks	final sample: 426
14	hyperemesis gravidarum.	on a website related to the topic	3 years	808 women
15	PTSD after birth	links on relevant websites		921 responses, 918 eligible
16	risk-perception of drugs and other exposures (2 publi-cations)	links on relevant websites	5 weeks	1821 responses, 1792 eligible

Table 1a – continuation.

Refe-rence	Topic	Recruitment	Recruitment period	Response
17	future pregnancy manage-ment after an unexplained stillbirth	on a website related to the topic	1 year	105 participants
18	delayed conception (several publications).	links on relevant websites and press release	from June 2007	2288 participants after 6 months
19	breast size	Invitation discussion-sites/ fora		120 completed surveys
20	premonition before stillbirth	links on relevant websites and press release	2 years	1034 women, 842 eligible
21	depression	nks to survey posted on relevant websites	7 months	100 eligible participants
22	influenza vaccination coverage	via the SurveySpot panel	22 days	response rate 91%, 1457 eligible
23	influenza vaccination coverage	via the SurveySpot panel	15 days	response rate 94%, 1660 eligible
24	influenza vaccination coverage	via the SurveySpot panel	13 days	response rate 93%, 1702 eligible
25	IVF practices	asked in clinic to complete on the spot		262 (98%) of 268
26	executive function in children	paper flyers and links on craigslist.org and on message boards.		final sample: 375
27	PTSD after birth	links on relevant websites and Internet support groups	6 months	final sample: 675
28	vaccination during pregnancy.	eligible women were sent a letter	4 months	3067 (21%) of 14529
29	birth induction based on age	Advertisement on website for mothers	24 hours	final sample: 663
30	health problems, medication use and information need (several publication)	links on relevant websites	2 months in each country.	total study population: 9459
31	acupuncture	by e-mail or letter		137 (51.7%) of 265
32	pregnancy after a perinatal loss	links on relevant websites and fora	5 months	88 respondents
33	Internet fora addressing miscarriage	links on relevant websites and fora	5 weeks	305 respondents
34	consumption and postpartum depression	e-mails and snowball sampling.	19 days	400 eligible surveys
35	dietary supplement use	via mass-media campaigns	over 3 years	903 pregnant women

Table 1b. Eligible Web-based Surveys Addressing Women Planning a Pregnancy, Being Pregnant or Having Given Birth, Published From 2000 to 2013, Investigating a Methodological Topic.

Refe-rence	Topic	Recruitment	Recruitment period	Response
18	recruiting a cohort via the Internet (2 of several publications)	links on relevant websites and press release	from June 2007	2288 participants after 6 months
36	the Edinburg Postnatal Depression scale	on a website about pregnancy and motherhood	3 weeks	492 responses, final sample: 440
37	recruitment and follow-up via the Internet	poster and distribution of leaflets via a hospital	1,5 year	687 responses, final sample: 670
38	comparison of methods of data collection. [a]	invitation by letter	8 months	3997 (64.3%), 506 by Internet
39	measure of control and support during birth	links on relevant websites and by snowball e-mails	Somewhere 2004-2005?	427 responses, 402 eligible
40	an eHealth program	Invitation by email	6 months	163 (43.4%) of 376 participants
41	comparison of information gained by Internet or interview	eligible women were sent a leaflet	14 months	159 (46%) responses, 106 by Internet
42	development of a psychological model	advertisements on Facebook	4 months	final sample: 344 women.
43	testing a mid-range nursing theory	links on pregnancy-related websites, fora and social media	3 months	143 eligible participants
44	efficacy of prenatal care	link to survey posted on relevant website	2 months	754 respondents

[a] There were more publications from this study, but they were not eligible for the review.

Table 1c. Eligible Web-based Surveys Addressing Women Planning a Pregnancy, Being Pregnant or Having Given Birth, Published From 2000 to 2013, Investigating Internet Use Related to Pregnancy and Health.

Refe-rence	Topic	Recruitment	Recruitment period	Response
45	the Internet as health information source	links on pregnancy-related websites	12 weeks	613 eligible participants
46	Internet use and web-based information	by phone		105 (75.5%) of 139
47	characteristics of mothers using online support groups	links on relevant message boards	8-months	final sample: 1006

The majority of the 37 publications discussed a health-related topic (n=25, 67.6%). Ten (24.3%) studies discussed a methodological topic (one study had several publications addressing health-related topics but also methodological issues and is counted in both groups) and three (8.1%) had investigated Internet use.

Table 2 shows the different recruitment methods used. Most studies used an open method of recruitment, like advertisement via the Internet itself (n=21, 56.8%) or via leaflets (n=1, 2.7%). The other 15 studies used a method addressing possible participants personally, allowing for the calculation of a response rate. Table 3 shows the country of residence of the participants of the several studies. All publications come from the US and Europe, except one from Australia. Figure 1 shows the number of publications we found per year. When there were multiple publications using the same dataset, we took the year of the first publication.

Figure 1. Number of Eligible Web-based Surveys Addressing Women Planning a Pregnancy, Being Pregnant or Having Given Birth per Year From 2000 – 2013.

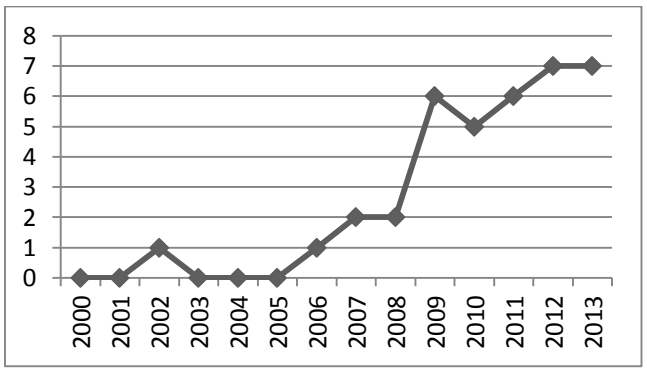

Table 2. Recruitment Methods Used in the Eligible Web-based Surveys Addressing Women Planning a Pregnancy, Being Pregnant or Having Given Birth, Published From 2000 to 2013.

Recruitment method	Number of publications ntot=37 n(%)	References
Internet	21 (56.8%)	11-21, 26, 27, 29, 30, 32, 33, 36, 39, 42, 43-45, 47
Links on websites related to topic	16	12-17, 21, 27, 29, 30, 32, 36, 39, 43-45
Fora / discussion groups	6	19, 27, 32, 33, 43, 47
Social media	2	42, 43
Showed when using search engine	1	11
Poster / leaflets	1 (2.7%)	37
Letter	2 (5.4%)	28, 38
Email	2 (5.4%)	34, 40
Personally asked	2 (5.4%)	25, 41
Phone	1 (2.7%)	46
Mixed	5 (13.5%)	18, 20, 26, 31, 35
Survey panel	3 (8.1%)	22, 23, 24

Table 3: Country of Residence of the Participants of the Eligible Web-based Surveys Addressing Women Planning a Pregnancy, Being Pregnant or Having Given Birth, Published From 2000-2013.

Country		Number of publications
Several countries; several languages		1
Several countries; English questionnaire		8
Residence research institute:	*US*	*4*
	United Kingdom	*3*
	Australia	*1*
English questionnaire; no information about origin participants		6
Residence research institute:	*United Kingdom*	*5*
	US	*1*
US		9
Netherlands		3
France (and other French-speaking countries)		3
Sweden		2
Italy		1
Norway		1
Denmark		1
Poland		1
Austria		1

Topics

In at least 16 of the 25 publications addressing a health-related topic, investigating women's perceptions about the topic is an important part of the aim of the study. Other purposes were to collect data for the investigation of a hypothesized association or to describe the study population. Methodological issues studied were mostly related to the recruitment method, mode of data collection or the measurement scale used.

Recruitment

Investigators used different methods for the recruitment of participants for the several studies (Table 2). Length of recruitment and recruited numbers are very different as well. Twenty-one studies used the Internet as main recruitment method. Adverts for the study with a link to the questionnaire were placed on websites, message boards or discussion platforms related to the topic investigated, either very broad, targeting pregnant women or recent mothers for example or rather narrow, targeting pregnant women with a certain condition. For these studies, the size of the targeted population is unknown and recruitment rate cannot be calculated.

The questionnaires of the studies using the Internet as main recruitment method were accessible from 24 hours until several years and these questionnaires were completed by 88 to 9,483 participants. A few publications did not mention the recruitment time [15,19,26,39] but for the studies that did, the number of participants recruited per day ranged from 0.4 to 663 with a mean number of recruited participants of 42.8 per day.

Validity and completeness of data collected

The questionnaires used for the studies investigated were very different. Some questionnaires were based on existing and validated pen-and-paper measurement scales and extensively tested before used as a web-based tool. Some contained parts of existing and validated measurement scales, sometimes slightly changed to match the topic investigated, together with some new questions. Other questionnaires were newly developed, either based on literature, peer discussions and/or patient focus group discussions and tested. Several publication did not mention any validation or testing before actual use. Number of questions ranged from 6 to at least 450 with questionnaires only containing multiple choice questions and Likert-scales and others with questions with free text entry. Results were hardly compared with data from existing databases, if present. Most studies compared the results they found with results from previous literature investigating a similar topic, but literature was not always available. Especially when a study investigated perception of pregnant women on a certain topic, little was known already. If compared, results largely corresponded to literature but some findings were new or different. Studies evaluating the method of data collection used found that incompleteness or errors often occur because participants did not understand certain questions. This was often solved by providing extra information or rephrasing the question.

Representativeness of the sample

Generally, study samples obtained in the studies investigated, were older, higher educated and more 'white' than the general pregnant population in the country where the study was originated or executed. The mean age of the women participating in the studies reporting mean age, ranged from 27.7-34.4. Demographics were not always shown in the publications and sometimes it was not clear if they were asked in the first place. Most studies addressed representativeness themselves, acknowledging the possible differences between study sample and the target population and the probability of selection bias due to the recruitment method used, but often state that for their objectives representativeness and generalizability is of minor concern or not thought to be worse than with observational studies using traditional methods for recruitment and data collection [16b,18a,22,35,37,38,42].

Discussion

All studies examined for this review collected data for epidemiologic research from women who wanted to get pregnant, were pregnant or had been pregnant, by using an online questionnaire. Most studies investigated women's' perceptions about a health-related topic or evaluated the method used.

In 2013 39% of all people worldwide used the Internet but regional differences are pronounced, ranging from 16% of people in Africa to 75% of European citizens [48]. This difference in Internet coverage is clearly apparent in the areas that were covered by the studies we examined. Internet surveys are predominantly used in Western countries, where Internet coverage is high. Internet use is still increasing over time as were the number of publications we found per year, but there will always be (sub)-populations that have limited access.

Within a country the use of Internet depends on age and socio-demographic factors like educational level and income [49]. Data shows that Internet use is significantly less for people over 65 years of age, but for women of reproductive age Internet access is high [49]. The chance of selectivity of the sample is increased by the fact that higher educated, white people are more likely to participate in an Internet survey as is confirmed by our results , but literature shows that web-responders do compare to responders by paper on most demographic variables when the same recruitment method is used for both groups [5,6].

Recruitment method influences the final composition of the sample [4,7]. For the studies we investigated, the one study using Facebook for recruiting participants obtained a sample of much younger age than the general pregnant population [42]. Several studies used websites, Internet fora or message boards on a specific topic of interest to show advertisements for their research. This will probably result in a sample of participants that are more engaged with the topic investigated. More severely or emotionally affected women will probably respond more often because they search for information and social support [14,15], leading to another type of selection bias. Language will also influence selectivity. Most questionnaires were only available in the dominant language of the country where the study was performed, comparable to the more traditional methods of data collection. Some studies did not ask or mention the country of residence of the people participating in their study. Internet sites used for recruiting participants can be accessed from all over the world and representativeness cannot be assessed if demographic variables are not asked. Most of the time it is hard to know if selection bias is apparent and affects the results, since little is known about the non-responders [50].

Literature shows that selection bias is likely to affect estimates like prevalence, but might not necessarily affect patterns of associations investigated [7,50].

Response rate can have an effect on the selectivity of a sample. A lower response rate is related to a bigger chance that non-responders differ substantially from responders [4]. Response rate often is impossible to determine if open recruitment is used, like advertisement on the Internet. Target population is often defined but numbers are not always known, and the percentage of the target population that can be reached by the recruitment methods used is not known either. To achieve an adequate number of random participants it is very important to use the right recruitment strategy. The studies we investigated used different recruitment strategies, different website to advertise on and had very different target populations. Recruitment numbers and methods are hard to compare, but differed significantly from 0.4 to 663 participants per day. Literature is inconclusive about the best recruitment method for Internet surveys. The right methods to use seem to depend on the topic investigated and the target population [1]. Fairly new approaches using social media seem to be able to attract a substantial number of participants within a short period of time, but these participants represent a highly selected population [42]. The continuous connection with the Internet of more and more people nowadays via mobile devices poses new opportunities in reaching possible participants, but may lead to a high number of drop-outs [51]. Recruiting an adequate sample of participants asks a lot of the creativity and Internet-literacy of the investigator.

We found no evidence of self-reported web-based data being more prone to incompleteness or non-validity than the same data collected via traditional methods like pen-and-paper, telephone surveys or interviews. When data could be compared to results from recent literature using other methods of data collection, results largely corresponded but completeness and validity are hard to judge because often no gold standard or other data sources are available, especially when perception is investigated. Literature suggests that epidemiologic data collected via the Internet is at least as reliable as data collected with more traditional methods. Because respondents feel more anonymous, they are less likely to give a more social desirable answer and data quality improves by the possibility of incorporating validation checks and avoiding data entry errors [5,6].

The Internet can be used for questionnaire-based studies to investigate perceptions of pregnant women or topics related to pregnancy assessing associations between variables and outcomes very well, providing the recruitment method used is efficient and well-targeted. Our study shows that several topics were covered already, but numbers of publications are still limited. Healthy pregnancy for mother and child is an important area of investigation and the possibilities of the Internet within this research are still elaborated. Recently for example, the PROTECT pregnancy study has been finalized [52].

The PROTECT pregnancy study aimed to explore new tools for data collection. Information was collected from pregnant women by the Internet on medication use and certain lifestyle factors throughout their pregnancy. Results might lead to an extended use of the Internet for the collection of data on risk-factors and other health-related data from pregnant women themselves.

Data obtained via open recruitment on the Internet is less suitable to calculate prevalences, but it can have its value in getting a first estimation. When assessing prevalences it is important to define the target population reached by the particular recruitment method used and to keep in mind that for a population with other characteristics, results might have differed subsequently. There is no evidence to suspect that validity and completeness of web-based data is worse than validity and completeness of data based on self-reporting, derived with traditional methods.

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Chapter 4.2 Lifestyle choices and pregnancy outcomes registered within the PROTECT pregnancy study.

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Abstract

Background

Data for epidemiological research on factors playing a role in the development of the fetus can be obtained in several ways. To explore the possibilities of collecting information about potential risk factors directly from pregnant women via the Internet, the PROTECT pregnancy study was started. In this paper we compared data about lifestyle factors and birth outcomes entered by the women participating in this study with figures of pregnant women in the general population of the participating countries.

Methods

The PROTECT pregnancy study ran in four countries: the United Kingdom, Denmark, The Netherlands and Poland. To assess the quality and completeness of the information provided by the pregnant women themselves, data about lifestyle factors and birth outcome were compared to national or regional data available in databases and literature.

Results

The PROTECT pregnancy study recruited a population that was mainly slightly older, higher educated and more health-focused than the average pregnant population and characteristics investigated varied highly between the participating countries. Where comparison was possible, data on birth defects matched poorly to data obtained from a birth registry.

Conclusion

In this study we found no evidence to question the validity and completeness of self-reported data via the Internet over data obtained via traditional survey methods or derived from health care workers or medical databases, except for data on birth defects obtained shortly after birth.

Introduction

Lifestyle choices made by a woman who is or could get pregnant can play a crucial role in proper development and the prevention of birth defects or other negative birth outcomes. Epidemiological studies are of great importance for the identification of the effects of lifestyle factors, medical conditions and medication use before and during pregnancy. Animal studies do not always predict negative birth outcomes in humans and for ethical reasons, pregnant women are excluded from clinical trials.

Data for epidemiological research on factors playing a role in the development of the fetus can be obtained in several ways. Health care providers or medical records can be consulted retrospectively. However, since this information was collected originally for medical reasons, data important for epidemiological research might be missing.

Another approach is to form a pregnancy cohort. Women planning a pregnancy or being pregnant are asked to join the cohort and provide information about their pregnancy, lifestyle choices, health and medication use. This information provided directly by the women themselves can be complemented with data from health care providers, medical records or tissue samples. Prospective data collection directly from pregnant women has several advantages. Since the pregnancy has not ended yet, women will remember their health and lifestyle choices and recall bias is avoided. Yet for a rare exposure to be associated with a rare outcome, the number of participants needed, will be very high.

Since the introduction of the Internet in the 1990s, researchers have discovered its possibilities for data collection in epidemiological research. Data collected by a web-based questionnaire can be saved in a database and checked for errors instantaneously, improving data quality [1,2]. Web-based questionnaires can be made situation-specific, passing irrelevant questions to increase convenience for the respondent [2]. Use of an appropriate recruitment strategy can increase response rate and save costs [2,3], but comparison to traditional methods is difficult because for questionnaires distributed via Internet population reached and response rate often cannot be determined [2]. Self-administration and completion of a survey via Internet has shown to be very suitable for sensitive topics, since participants tend to answer more honest being anonymous, with less social desirability [1,4].

The use of the Internet for collecting epidemiological data can have some drawbacks though. In 2013, it was reported that 39% of the population worldwide had access to the Internet, ranging from 16% of the African population to 75% of European citizens [5].

Numbers are still increasing, but the population of people using the Internet differs from the population without access, which may lead to selection bias and non-generalizability presumably due to the higher socioeconomic status and education [6]. The question is whether and how a sample acquired via Internet will differ from a sample recruited via traditional methods [1,7]. Furthermore, despite negating evidence researchers might still have worries about the validity and completeness of data collected via the Internet by self-reporting [1].

The PROTECT pregnancy study was created to evaluate the potential contribution of collecting information on medication use and other potential risk factors directly from pregnant women via the Internet for research purposes. This European study was run in four countries: United Kingdom (UK), Denmark, The Netherlands and Poland. It is a non-interventional, prospective study where pregnant women were asked to provide information about their health, lifestyle factors and medication use in their current pregnancy. In this paper we investigate whether a database like the PROTECT pregnancy study can be used to explore potential relationships between lifestyle factors and birth outcomes. We assess the agreement between lifestyle factors and birth outcomes reported by the women participating in PROTECT, with figures of pregnant women in the general population of the participating countries.

Methods

To attract pregnant women in the four participating countries to enroll in the PROTECT pregnancy study, several recruitment strategies were used, varying per country. Recruitment included advertisement on pregnancy related websites and social media, leaflets displayed at obstetric units and pharmacies in the Netherlands and the UK, emails sent to registered users of pregnancy related and parenting websites and a media campaign in Poland. Further details about recruitment were described elsewhere [8]. We aimed to recruit women as early in pregnancy as possible but pregnant women in all stages of pregnancy were able to join when at legal age to consent to participate (18 years for Denmark, the Netherlands and Poland and 16 years for the UK).

After enrolment women were asked to complete a baseline questionnaire to provide demographic information, information about their health and lifestyle, their pregnancy and medication use just before and during this pregnancy. On a periodic basis participants were asked to up-date this information, and when the pregnancy had ended, to fill in a short questionnaire about the pregnancy outcome. Participants were able to provide the information via the Internet and had to choose whether to give an update of their information every two or every four weeks, at their choice.

The lifestyle factors and pregnancy outcomes collected in the PROTECT pregnancy study and investigated in this paper are listed in Table 1. These variables were selected to include the most important variables known to influence pregnancy and birth outcome, based on literature so far. For medication use for chronic conditions, we focused on medication for common chronic conditions because it has been shown that chronic medications are recalled and reported more adequate than short-term medications [9] and because of the possible effects of the use of these medications on the fetus.

To assess the representativeness of the study sample and evaluate the quality and completeness of the information provided by the pregnant women themselves, data about lifestyle factors and birth outcome were compared to national or regional data available, using the Pearson's X2 test for comparison. Variables were compared to reference data from offices for national statistics, birth registries, pharmacy databases or available publications showing prevalences of the characteristics under study in the target populations, whatever provided the most suitable information. When available, variables were compared to a maximum of two reference populations.

Table 1: lifestyle factors and pregnancy outcomes investigated.

Variables	Pregnancy outcomes
Age at time of delivery	Singleton/multiple pregnancies
Parity	Gestational age
Planning of pregnancy	Birth weight
BMI	Congenital anomalies
Smoking	
Alcohol use	
Use of folic acid	
Use of multivitamins	
Use of Iron supplements	
Use of fertility medication	
Medication use for chronic conditions	

Results

The PROTECT pregnancy study was open for participation from October 2012 until March 2014. In total 2520 women enrolled in the study. 2065 (81.9%) of the women completed the baseline questionnaire, 639 from Denmark, 476 from the Netherlands, 241 from Poland and 709 from the UK. Of these enrolled women 1555 (75.3%) had their expected end of pregnancy date within the study period and should have been able to provide outcome data. Nearly thirty percent (464, 29.8%) provided information about childbirth and the health of their baby.

Table 2: Maternal characteristics and lifestyle.

		PROTECT n(%)	n-tot:	between countries p-value	Reference n(%)	n-tot:	PROTECT vs ref. p-value
age at time of	DK	382 (59.8)	639		31171 (56.4)[1]	55225	0.091
delivery 35	NL	293 (61.6)	476		97944 (57.6)[2]	170093	0.080
years and older	PL	102 (42.3)	241		161879 (43.6)[3]	370962	0.681
	UK	454 (64.0)	709	**<0.001**	352964 (50.5)[4]	698512	**<0.001**
nullipara	DK	245 (38.6)	635		25588 (46.7)[1]	54836	**<0.001**
	NL	225 (47.8)	471		77647 (44.9)[2]	173099	0.204
	PL	112 (49.8)	225		175658 (47.4)[3]	370962	0.466
	UK	295 (41.8)	706	**0.003**	38653 (42.4)[5]	92218	0.944
bmi before	DK	223 (34.9)	639		20076 (37.6)[1]	53375	0.159
pregnancy	NL	170 (35.7)	476		47 (21.7)[8]	217	**<0.001**
> 25	PL	40 (17.2)	233		118 (19.9)[7]	592	0.364
	UK	324 (46.4)	698	**<0.001**	43343 (48.0)[5]	90350	0.413
pregnancy	DK	485 (78.5)	618		199 (77.1)[9]	258	0.660
being planned	NL	401 (85.3)	470		389 (75.5)[6]	515	**<0.001**
	PL	158 (73.1)	216				
	UK	532 (75.6)	704	**<0.001**			
educational	DK	246 (38.8)	634		8201 (15.5)[1]	52759	**<0.001**
level 4	NL	183 (38.4)	476		45 (8.8)[6]	511	**<0.001**
(university,	PL	158 (66.1)	239				
master)	UK	213 (30.2)	706	**<0.001**			
	DK	26 (4.3)	606		5471 (10.0)[1]	54591	**<0.001**
smoking at	NL	20 (4.4)	436		130 (25.2)[6]	515	**<0.001**
baseline	PL	11 (4.7)	234		507 (9.72)[10]	5214	**0.010**
	UK	34 (4.8)	706	0.969	17834 (19.3)[4]	92218	**<0.001**
alcohol use at	DK	173 (27.2)	637		40998 (44.6)[11]	91843	**<0.001**
baseline	NL	33 (7.0)	474		195 (37.9)[6]	515	**<0.001**
	PL	28 (11.7)	239		561 (15.3)[12]	3662	0.132
	UK	233 (33.0)	705	**<0.001**	7281 (8.2)[5]	88569	**<0.001**

1 Danish Birth Registry 2013

2 Stichting Perinatale Registratie Nederland: Perinatale Zorg in Nederland 2012

3 Central Statistical Office of Poland (GUS) 2013

4 Office for National Statistics (ONS) 2013

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14 Daemers et al: Patterns of gestational weight gain in healthy, low-risk pregnant women without co-morbidities. Midwifery 2013;29:535-541. (first trimester BMI)

Maternal characteristics

Table 2 shows the outcomes for the maternal characteristics that were investigated. Most variables differ significantly between the participating countries. Polish participants were the youngest (mean age at birth: 29.8) and UK participants the oldest (31.7), Denmark had the least nullipara (39%), while Poland had the most (50%), Poland had the least overweight participants (17%), while the UK had the most (46%), for Poland least pregnancies were planned (73%), while the Netherlands had highest proportion of planned pregnancies (85%). Uk participants were least educated, 30% had a master or university degree, while Polish participants had the highest education (66%). The number of participants that smoked at the time they completed the baseline questionnaire corresponded fairly well between the four countries with a mean percentage of 4.5%. Data on alcohol use varied a lot though, ranging from 7.0% of Dutch participants indicating to have used alcohol during their current pregnancy, to 33.0% in the UK.

Comparing maternal characteristics to national or regional data when available, did not give a univocal picture. Age data only differed for the UK, parity did for Denmark, BMI and planning of pregnancy was different for the Netherlands compared to other countries. Educational level, smoking and alcohol use at time of baseline completion seems to differ most between the countries and also with data from reference sources.

Medication use

Data about folic acid use, either by itself or in multivitamins, iron supplement use and the use of fertility medications are shown in Table 3, while Table 4 shows the results on medication use for the chronic diseases investigated. The use of folic acid at the time of baseline completion is quite high, but differs between countries with Poland showing the lowest rate (74.7%) and the Netherlands the highest (94.4%).

Poland also shows a lower use of multivitamins for all women that were followed throughout pregnancy (57.1%), while multivitamin supplementation was considerably higher for Danish participants (89.8%). The use of fertility medication to establish current pregnancy also differed between participating countries, ranging from 6.1% in the UK to 11.6% in the Netherlands, the latter being much higher than data from a prescription database (0.7%). Comparison data for supplement use were scarce, but data on folic acid and multivitamin use in the PROTECT pregnancy study were significantly different from data available in literature. Remarkably, compared with published rates, multivitamin use for the Netherlands and the UK was lower than found in our study, while for Poland it was considerably higher.

Table 3: Supplement use and use of fertility medication

		PROTECT n(%)	n-tot:	between countries p-value	Reference n(%)	n-tot:	PROTECT vs ref. p-value
use of folic acid	DK	562 (87.9)	639				
(either alone or in	NL	458 (96.2)	476		452 (87.8)[1]	515	**<0.001**
multivitamin)	PL	180 (74.7)	241				
baseline	UK	669 (94.4)	709	**<0.001**			
use of	DK	132 (89.8)	147				
multivitamins	NL	66 (75.0)	88		570 (58.6)[2]	972	**0.003**
entire pregnancy	PL	20 (57.1)	35		1324 (87.7)[2]	1510	**<0.001**
	UK	109 (72.2)	151	**<0.001**	488 (55.0)[2]	887	**<0.001**
use of iron	DK	121 (82.3)	147		41971(77.2)[3]	54371	0.140
supplements	NL	11 (12.5)	88				
entire pregnancy	PL	13 (37.1)	35				
	UK	33 (21.9)	151	**<0.001**			
use of fertility	DK	57 (8.9)	639		21 (8.1)[4]	258	0.707
medication	NL	55 (11.6)	476		77 (0.7)[5]	10955	**<0.001**
baseline	PL	22 (9.1)	241				
	UK	43 (6.1)	709	**0.010**			

1 Zetstra - van der Woude et al: Periconceptional folic acid use: still room to improve. Birth Defects Res A Clin Mol Teratol 2012;94(2):96-101.
2 Oliver et al: Dietary Habits and Supplement Use in Relation to National Pregnancy Recommendations: Data from the EuroPrevall BirthCohort. Matern Child Health J 2014;18(10):2408-2425.
3 Knudsen et al: Iron supplement use among Danish pregnant women. Public Health Nutr. 2007;10(10):1104-1110.
4 Backhausen et al: Pregnancy planning and lifestyle prior to conception and during early pregnancy among Danish women. Eur J Contracept Reprod Health Care. 2014 Feb;19(1):57-65.
5 IADB.nl (2008-2012)

For the use of all chronic medications investigated there were considerable differences between the participating countries, except for the use of antiepileptics but the latter is probably due to low numbers (Table 4).

Table 4: Medication use for chronic conditions

		PROTECT n(%)	n-tot:	between countries p-value	Reference n(%)	n-tot:	PROTECT vs ref. p-value
Antidiabetics	DK	2 (0.3)	639		384 (0.7)[1]	54314	0.236
insulin	NL	7 (1.5)	476		185 (1.7)[2]	10955	0.717
Atc: A10A	PL	6 (2.5)	241				
	UK	20 (2.8)	709	**0.003**			
Antidiabetics	DK	12 (1.9)	639		532 (1.0)[1]	54314	**0.023**
oral	NL	0	476		14 (0.1)[2]	10955	0.435
Atc: A10B	PL	3 (1.2)	241				
	UK	27 (3.8)	709	**<0.001**			
Thyroid medication	DK	18 (2.8)	639		1250 (2.3)[1]	54314	0.388
Atc: H03	NL	19 (4.0)	476		229 (2.1)[2]	10955	**0.005**
	PL	21 (8.7)	241				
	UK	22 (3.1)	709	**<0.001**			
Antidepressants	DK	46 (7.2)	639		1739 (3.2)[1]	54314	**<0.001**
Atc: N06A	NL	17 (3.6)	476		313 (2.9)[2]	10955	0.362
	PL	3 (1.2)	241				
	UK	56 (7.9)	709	**<0.001**			
Antiepileptics	DK	10 (1.6)	639		352 (0.6)[1]	54314	**0.004**
Atc: N03	NL	2 (0.4)	476		35 (0.3)[2]	10955	0.705
	PL	2 (0.8)	241				
	UK	6 (0.8)	709	0.259			
Antiasthmatics	DK	40 (6.3)	639		2061 (3.8)[1]	54314	**0.001**
Atc: R03	NL	30 (6.3)	476		564 (5.1)[2]	10955	0.266
n (%)	PL	7 (2.9)	241				
	UK	68 (9.6)	709	**0.002**			
COMPARISON WITH SECOND REFERENCE,WHEN AVAILABLE							
Antidiabetics	DK	2 (0.3)	639		(0.6)[3]	~5 M	
insulin	NL	7 (1.5)	476		(1.1)[3]	~500 K	
Atc: A10A	PL	20 (2.8)	709		(1.0)[3]	~5 M	
Antidiabetics	UK	12 (1.9)	639		(0.7)[3]	~5 M	
oral	NL	0	476		(0.1)[3]	~500 K	
Atc: A10B	UK	27 (3.8)	709		(0.6)[3]	~5 M	
Antidepressants	DK	46 (7.2)	639		(2.3)[4]	320846	**<0.001**
Atc: N06A	NL	17 (3.6)	476		(2.3)[4]	13935	0.072
	UK	56 (7.9)	709		(3.7)[4]	182920	**<0.001**
Antiepileptics	DK	10 (1.6)	639		1497 (0.5)[5]	324134	**<0.001**
Atc: N03	NL	2 (0.4)	476		64 (0.4)[5]	14725	0.962
	UK	6 (0.8)	709		1209 (0.6)[5]	207570	0.949

1 Danish Birth Registry 2013

2 IADB.nl 2008-2012

3 Charlton et al: EUROCMEDICAT deliverable 28 [WP6]. Available via http://euromedicat.eu/

4 Charlton et al: Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. BJOG. 2015 Jun;122(7):1010-1020.

5 Charlton et al: Antiepileptic drug prescribing before, during and after pregnancy: a study in seven European regions. Pharmacoepidemiol Drug Saf. 2015 Aug 13 [Epub ahead of print].

Some of the chronic medication was used for different indications in the different countries. The oral anti-diabetic drug metformin was used with polycystic ovary syndrome (PCO) in Denmark (10 out of 12 users) and the UK, but not in the Netherlands and Poland. Aside from epilepsy, antiepileptics were also used for other indications as bipolar disease, anxiety and migraine prevention in Denmark and for hepatitis in Poland. For Denmark and the Netherlands we were able to compare the data on chronic medication use with registry data. Comparison showed several statistically significant differences between the self-reported data of PROTECT and pharmacy dispending data registered in the DBR or IADB.nl, all with higher medication use for the PROTECT data.

Table 5: Multiple births, gestational age and birth weight for women with a live birth that completed the outcome questionnaire.

		PROTECT n(%)	n-tot:	between countries p-value	Ref n(%)	n-tot:	PROTECT vs ref. p-value
multiple births	DK	1 (0.7)	147		1168 (2.1)[1]	55225	0.227
n (%)	NL	2 (2.3)	88		2992 (1.7)[2]	173099	0.695
	PL	1 (2.9)	35		9935 (2.7)[3]	370962	0.948
	UK	4 (2.6)	151	0.148	10783 (1.6)[4]	690820	0.281
gestational age	DK	3 (2.5)	121		1695 (3.2)[1]	53149	0.657
<36wk singletons	NL	7 (9.3)	75		6074 (3.6)[2]	167965	**0.008**
n (%)	PL	1 (3.3)	30				
	UK	1 (0.8)	124	**0.013**			
birth weight	DK	3 (2.1)	145		1951 (3.7)[1]	52816	0.300
<2500 gr	NL	7 (8.4)	83		8268 (4.9)[2]	169977	0.131
singletons	PL	3 (8.8)	34				
n (%)	UK	2 (1.4)	147	**0.011**			
COMPARISON WITH SECOND REFERENCE, IF AVAILABLE							
gestational age	DK	3 (2.5)	121		(4.8)[5]	60667	0.233
<36wk singletons	NL	7 (9.3)	75		(5.8)[5]	170404	0.191
n (%)	PL	1 (3.3)	30		(5.3)[5]	402171	0.631
	UK	1 (0.8)	124	**0.013**	(5.6)[5]	689420	**0.020**
birth weight	DK	3 (2.1)	145		(3.5)[5]	60506	0.349
<2500 gr	NL	7 (8.4)	83		(4.6)[5]	171568	0.096
singletons	PL	3 (8.8)	34		(4.4)[5]	402170	0.209
n (%)	UK	2 (1.4)	147	**0.011**	(5.5)[5]	691181	**0.028**

1 Danish Birth Registry 2013

2 Stichting Perinatale Registratie Nederland: Perinatale Zorg in Nederland 2012

3 Central Statistical Office of Poland (GUS) 2013

4 Office for National Statistics (ONS) 2013

5 EURO-PERISTAT. – Better statistics for better health for pregnant women and their babies. European perinatal health report. Available from: http://www.europeristat.com, for the UK only data from England and Wales

Pregnancy outcome

Pregnancy outcome is shown in Table 5. For all 421 pregnancies with a reported live birth, 1.9% was a twin birth. The mean gestational age of singletons was 39.6 weeks (SD: 2.1), ranging from 39.1 in the Netherlands to 39.8 in Denmark and the UK. Mean birth weight ranged from 3201 gram in Poland to 3494 in the UK with an overall mean of 3454 gram (SD: 580). The proportion of singletons with a gestational age under 36 weeks (0.8-9.3%) as well as the proportion of singletons with a birth weight under 2500 grams (1.4-8.8%) was significantly different between participating countries, but numbers were low.

Table 6 shows all congenital malformations reported for live born infants in PROTECT and compares self-reported and clinical terminology. For 2.3% (n=10) of all children, the mother reported that her baby had a birth defect. Two were excluded, since the 'defect' mentioned was not a real birth defect or remained to be confirmed. When asked for any other information, a birth defect was reported for another 5 children, adding up to 3.0% (n=13) of children with a reported live birth. The birth defects that were not mentioned as such were predominantly mild malformations (3 ankyloglossia, 1 hypospadias, 1 malformation of the ear).

Table 6: Congenital malformations reported, among live births

	n	Terms used by participants	Malformation according to ICD-10
DK	4	pendant of the neck	congenital malformation of face and neck, unspecified
		cleavage of the foreskin, urethra ends 1 mm too low, string is too short	hypospadia, balanic
		lymphatic malformation of the tongue	other congenital malformation of tongue
		bottom of her right ear does not attach	other congenital malformation of ear
NL	2	string of tongue too short, tongue heart-shaped	ankyloglossia
		urethra ends a little lower	hypospadia, unspecified
PL	1	malformation of the 4th phalanx of the left hand	congenital absence of unspecified hand and finger
UK	6	heart murmur	congenital malformation of heart, unspecified
		tongue tie	ankyloglossia
		tongue tie	ankyloglossia
		minor tongue tie	ankyloglossia
		trisomy 21;	Down syndrome, unspecified;
		bilateral talipes	congenital deformity of feet, unspecified
		sebaceous cyst	pilar and trichodermal cyst

For the Netherlands, EUROCAT NNL registered a total prevalence rate of major birth defects of 2.6% for all births (live births, fetal deaths and terminations) over the period of 2008-2012 [10].

Most common were the heart defects with a total prevalence of 0.8%, but the PROTECT numbers were too low for comparing subgroups of birth defects. The large number of ankyloglossia registered for the UK (2.6%) is noticeable, but since it is not a major birth defect, it is not registered in EUROCAT.

Mothers who reported a birth defect sometimes used a lay term while other malformation were described in medical terms. Generally, it was clear what the mother meant and what malformation the child was born with.

For Denmark, reported birth defects in PROTECT were compared to the Danish Birth Registry (DBR). We were able to match 120 children based on the civil registration number of the mother and results are shown in Table 7.

Table 7: Congenital anomalies Danish participants for the women that completed the outcome questionnaire (n=153)

		n
Number of malformation reported in Protect pregnancy study :		4
Number of malformations reported in Danish Birth Registry :		8
	malformation:	
Reported in Protect as well as in the DBR	hypospadia	1
Malformation in DBR, not in PROTECT (ntot=8)*	ankyloglossia	1
	cardiovascular defect(s)	1
	cerebral cysts	1
	hip dislocation	4
	undescended testis	1
Malformation in PROTECT, not in DBR (ntot=3)	neck malformation	1
	tongue malformation	1
	eye malformation	1

* For one child 2 different birth defects were registered.

In the PROTECT study, a birth defect was reported for 4 (2.7%) of the Danish children. For the 120 children we were able to trace in the Danish Birth Registry, 8 children (6.7%) had a reported birth defect. Only one of these birth defects was recorded in the PROTECT database as well. For Denmark, reported birth defects in PROTECT were compared to the Danish Birth Registry (DBR).

Discussion

The PROTECT pregnancy study recruited a selected population and characteristics investigated varied highly between the participating countries. Women participating in PROTECT were at average older, more highly educated and more health-focused than the average pregnant population in the participating countries according to their lower smoking and alcohol use at baseline.

PROTECT participants also planned their pregnancy more often and generally took folic acid supplements and multivitamins more often. Except for diabetes, PROTECT participants tend to use medication for different chronic conditions during their pregnancy more often. Pregnant women with a chronic condition that needs medication might feel more addressed by the notification of a study focusing on medication use during pregnancy. Literature on studies using web-based questionnaires for topics regarding pregnancy showed to attract women that were on average higher educated and less ethnically diverse with a predominantly white population compared to the target population, next to other varying differences [11-14].

The composition of the study sample will be determined by Internet access of the target population [15], a subpopulation not having access to the Internet might lead to 'coverage bias'. However, Internet access hardly is a restricting factor in Western countries nowadays. For 2011, Internet use ranged from 93% of all individuals in Poland to 99% in the Netherlands in the four participating countries [16]. Traditional survey modes like telephone interviews and pen-and-paper questionnaires tend to attract selected populations as well. Literature shows that participants completing a web-based questionnaire correspond to pen-and-paper participants considering age, education and health status when both groups are recruited univocally [1,3].

The characteristics of a study sample will be influenced by the recruitment method used [2,15]. The four countries participating in PROTECT each used different major recruitment strategies [8], which probably contributed to the differences in sample characteristics and sample selection. The main approach in Denmark was by web-advertisement leading to a sample recruited early in pregnancy, while in the Netherlands and the UK the main focus was with emails sent to registered users of pregnancy related websites who usually register in the second half of their pregnancy. Poland was the only country that used advertisements on television and parental classes to reach pregnant women.

Literature suggests that the Internet can be very suitable for collecting information on sensitive topics like smoking and alcohol use during pregnancy, since participants tend to answer more honest when staying anonymous [1,4].

Web-based data therefore are more likely to show a higher percentage of women to smoke or use alcohol during pregnancy than traditional methods do. However, our PROTECT data on smoking and alcohol use shows to be quite low (Table 2). Because of the absence of population data on these topics, validity of data on smoking and alcohol use during pregnancy is very hard to establish and when available, data in literature differ a lot due to differences in study design and selectivity of the study sample obtained. For the UK for example, data on smoking during pregnancy ranged from 6.9% [17] in a web-based survey to 20.9% [18] for a cohort where pregnancy notes from health care workers were used. For Poland percentages found in literature were around 10% , but a study measuring cotinine in saliva, an indicator for actual smoking, reported 16% of participating pregnant women to smoke. Data about prevalences of alcohol use during pregnancy are scarce and vary even more. A survey among obstetrician and gynecologist in a Dutch rural area reported a maternal alcohol use of 4.0% [19], while another survey in an urban area with self-reported alcohol use during first trimester of pregnancy reported a percentage of 41.8% [20]. In Denmark two studies investigated alcohol use during pregnancy both based on data from the Danish National Birth Cohort. The first reported 44.6% of pregnant women to have used alcohol during first trimester while the other showed alcohol use to be 88.7% during the entire pregnancy [21,22].

Data on smoking and alcohol use provided by the participants of the PROTECT pregnancy study probably is an underestimation of actual figures of these exposures among pregnant women in the participating countries, probably due to the self-selection of higher educated, more health-oriented women. Despite the anonymity of the web-based approach that discourages social desirable answering, some underreporting might be left. Literature shows that reliability of epidemiologic data collected via the Internet is comparable to that of data collected with more traditional methods [1,3].

For outcome data, numbers were quite too low to assess validity and completeness. For multiple births, population based percentages for 2010 ranged from 1.3 for Poland to 2.1 for Denmark [23]. National statistics data over 2013 showed a percentage of multiple births in the UK of 1.6 [24] and for Poland a percentage of 2.7 is given [25]. The overall number of women with a multiple birth in the PROTECT pregnancy study of 1.9% appears to correspond fairly well to these percentages, but numbers are too small to make a valid country based comparison.

When a child is diagnosed with a birth defect, women are very capable of indicating the birth defect present, whether in lay or medical terms. Nevertheless, self-reporting shortly after birth might not be a good method to obtain valid and complete information about possible birth defects of the baby. Some malformations registered within the Danish Birth Registry might have been detected after completion of the outcome questionnaire.

Hip malformations for example do not always show right after birth and heart defects and cerebral cysts might be detected later as well. Some small malformations like ankyloglossia and undescended testis are not considered as a major birth defect by EUROCAT but might be mentioned by the mother anyway.

Collection of data from pregnant women by self-reporting via the Internet is a good way of obtaining data about lifestyle choices. The lack of population data as a gold standard and the diversity of data found in literature shows the difficulty of establishing the validity of lifestyle data reported. We found no conclusive evidence to undervalue the validity and completeness of self-reported Internet-derived data compared to data obtained via traditional survey methods or derived from health care workers or medical databases, except for data on birth defects. Differences with national data, data from registries and data from literature might as well reflect the selectivity of the sample recruited via Internet. The selectivity of the sample limits the generalizability of prevalence data found. However, representativeness is not indispensable when investigating associations between exposure and outcome and might even be counterproductive when assessing rare exposures or outcome [15,26]. Data about birth defects derived from healthcare databases is probably more accurate than information obtained from the mother shortly after birth.

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Chapter 4.3 A study investigating the perceptions of women about the use of their asthma medication during pregnancy and the safety for their baby.

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Abstract

Objective

To investigate the perceptions of pregnant women about the risks of their asthma and asthma medication for their offspring, we used a web-based survey.

Methods

A web-based questionnaire was developed and pregnant women with asthma were recruited via two different routes to provide information about asthma control and management before and during pregnancy and about the information they got on risk of asthma and asthma medication for the unborn child.

Results

Our final sample consisted of 53 respondents. Among the 41 women with a planned pregnancy, 16 (39%) had their pregnancy wish discussed with a physician in relation to their asthma management and 12 (75%) had their asthma medication adjusted accordingly. Eight out of 22 women (36%) planning their pregnancy but discussing nor adjusting their medication beforehand, adjusted their asthma medication when pregnant because of possible risks for their infant. This was advised by their physician to 6 (75%) of them. Of the 22 women adjusting their asthma medication on advice of their physician because of health concerns for the infant, 12 (55%) experienced a worsening of asthma symptoms in response. Twenty-three out of 50 women (46%) had worries about the right choices regarding their asthma medications for the health of their infant and 16 women (32%) thought that the information they got or found was contradictory.

Conclusion

The counselling of women with asthma who want to become pregnant can be improved. There is a need for properly worded information about the importance of adequate asthma control in pregnancy to asthmatic fertile women irrespective of a current pregnancy wish.

Introduction

An increasing number of pregnancies is complicated by the presence of a maternal chronic condition and its pharmacological treatment [1]. For many drugs on the market potential risks for the unborn child cannot be fully determined yet, due to limited research or contradictory results of post marketing surveillance. However, untreated or undertreated maternal diseases can also have negative effects on the unborn baby leading to questions about the safest approach of disease management for both mother and child.

Asthma is one of the most frequent chronic maternal conditions complicating pregnancy. Prevalence estimates vary by region with up to 12% of pregnancies affected [2]. While negative effects of asthma medication on the unborn child have shown to be minimal [3], uncontrolled asthma during pregnancy is associated with significant risks for the mother as well as the infant, including preeclampsia, preterm labour, low birth weight, and being born small for gestational age [4,5]. Current international guidelines on the treatment of asthma therefore recommend optimal asthma control during pregnancy [6,7]. Still many women stop or change their asthma medication when pregnant, possibly leading to asthma exacerbation and concurrent increased risks for adverse pregnancy outcomes [6-10].

We conducted a descriptive survey to investigate the perceptions of pregnant women about the risks of their asthma and asthma medication for their infant, how they perceived the information about this topic given by their physician, and their motives for possible medication changes around the pregnancy period.

Methods

For this cross-sectional study among pregnant women with asthma, we developed a web-based questionnaire, which assessed several maternal characteristics including age, level of education, ethnicity, gravidity, and gestational age at completion. Information about asthma control and management before and during pregnancy was collected by asking about asthma medication (inhalation) used in the year before pregnancy, atopy and concurrent medication, consulting of a physician when planning a pregnancy, changes in asthma medication because of pregnancy wish and after confirmation of pregnancy, reasons for changes, the effects on asthma control, and course of asthma during pregnancy up to then. In addition, participants were asked about perceived risks of asthma and asthma medication for the unborn child and how they valued the information about asthma management during pregnancy by showing a couple of propositions. Propositions presented are shown in appendix 6.

Current asthma control was measured using the first 6 questions of the Asthma Control Questionnaire (ACQ) [11].

We recruited participants via two different routes. Firstly, the questionnaire was uploaded using Qualtrics Research Suite software and was online from June 2014 until June 2015. The Dutch patients' association for people with chronic lung disease (The Lung Foundation Netherlands; Longfonds), showed an announcement of this study on their website (www.longfonds.nl) during this period with a link to the questionnaire on the survey website. Secondly, we approached women participating in the PRegnancy and Infant DEvelopment (PRIDE) Study who reported to be diagnosed with asthma and were still pregnant. Details of this ongoing prospective cohort study can be found elsewhere [12]. In May 2014 and April 2015, an e-mail was sent to 71 women to ask them to complete the additional questionnaire for the current study.

Results

The questionnaire was opened 23 times through the website of The Lung Foundation Netherlands, A total of 15 women started to answer the questions of whom 11 completed the entire questionnaire. Of the 71 PRIDE Study participants approached, 6 were ineligible (three women had childhood asthma only, two participated through paper-based questionnaires, and one had a miscarriage) and 38 completed the questionnaire (response rate 58%). Therefore, the final sample of this study consisted of 53 respondents. Women recruited through the PRIDE Study were on average older, had a lower level of education and a higher gestational age at questionnaire completion than women recruited via open web-advertisement (Table 1).

Most questions about the level of asthma control, medication use, perception of risks, and information about asthma management were completed by 50 respondents. For 35 (71%) respondents the general practitioner was the physician monitoring their asthma. Ten women (20%) were under control by a pulmonologist, 1 (2%) by her gynaecologist, and for 3 (6%) women the asthma was not monitored at the moment. Asthma was well controlled in the year before pregnancy according to 46 (92%) respondents. In the year before pregnancy, 44 (88%) respondents used asthma medications, which are shown in Table 2. Allergic symptoms were accompanying the asthma for 41 (82%) respondents and 23 (56%) of them were using medications to treat these symptoms. During pregnancy up to questionnaire completion, asthma symptoms did not change for the majority of women (n=29, 58%). However, asthma symptoms got worse for 15 (30%) and improved for 6 (12%) women.

At the moment of completion of the questionnaire (mean gestational age 23 weeks), asthma was well or fully controlled for 37 (76%) respondents, moderately for 8 (16%), and poorly or very poorly controlled for 4 (8%) respondents.

Table 1: Maternal characteristics study sample

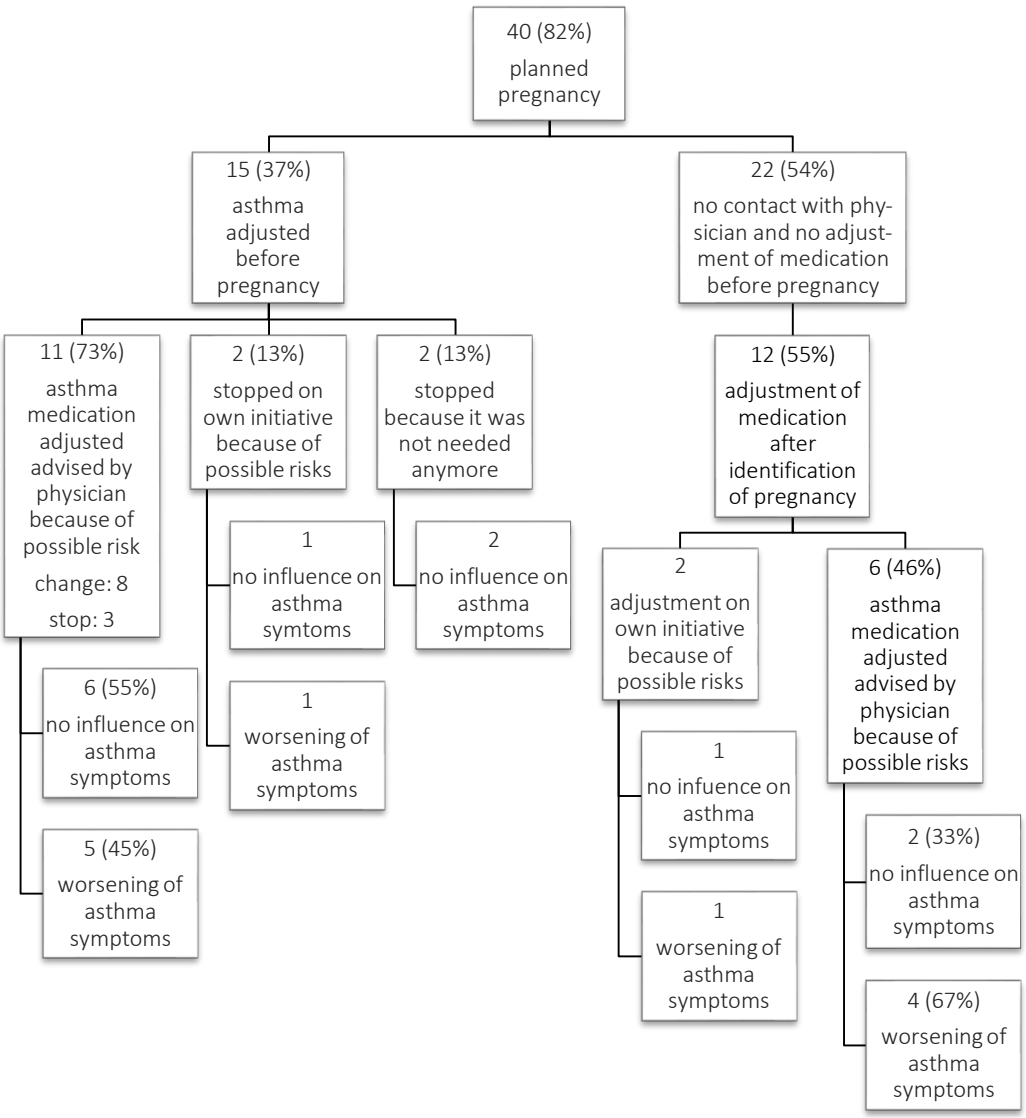
		total sample n-tot=53 n(%)	The Lung Foundation Netherlands n-tot=15 n(%)	PRIDE n-tot=38 n(%)	p-value
age (mean, sd)		29.0 (4.4)	27.2 (6.5)	29.7 (3.1)	0.170
educational level	low	4 (7.5)	3 (20.0)	1 (2.6)	
	middle	11 (20.8)	0	11 (28.9)	
	high	38 (71.7)	12 (80.0)	26 (68.4)	0.012
first pregnancy	yes	33 (62.3)	11 (73.3)	22 (57.9)	
	no	20 (37.7)	4 (26.7)	16 (42.1)	0.296
weeks pregnant (mean, sd)		23.1 (8.6)	19.1 (7.4)	24.8 (8.7)	0.028

Table 2: Asthma medication taken by the respondents in the year before pregnancy

medication (generic)	n	%
total (N = 50)	44	88.0
salbutamol	36	72.0
combination: salmeterol/fluticasone	9	18.0
combination: formoterol/budesonide	8	16.0
combination : formoterol/beclometasone	2	4.0
fluticasone	9	18.0
beclometasone	5	10.0
budesonide	3	6.0
ciclesonide	1	2.0
tiotoprium	1	2.0
formoterol	2	4.0
montelukast	2	4.0

Figure 1 shows a flowchart of the medication choices made by the responding women. Forty-one respondents (82%) had their pregnancy planned and 15 (37%) adjusted their asthma medication when planning their pregnancy, 7 of them stopped taking their medication when trying to get pregnant, and the other 8 changed one or more of their asthma medications into another.

Figure 1: flow-chart of decisions and medication adjustments made by responding women (n-tot = 50).



Two women adjusted their medication because they thought it would be better for the infant; 11 (73%) adjusted their medication in response to the advice of their physician that it would be better for the infant. For 9 (60%) women adjusting their medication, the adjustment had no influence on their asthma symptoms, while for the other 6 (40%) the asthma symptoms worsened.

Of all women planning their pregnancy, 16 (39%) had their pregnancy wish discussed with a physician in relation to their asthma treatment and 12 (75%) of them adjusted their asthma medication. Ten of them (63%) adjusted their medication on advice of their physician because of possible risks. Twenty-two women planned their pregnancy but did not discuss this pregnancy wish in relation to their asthma treatment with a physician nor adjusted their medication when planning their pregnancy. However, 8 of them (36%) adjusted their asthma medication when pregnant, because they thought it would be better for their infant; this was advised by their physician to 6 (75%) of them. Three (38%) women adjusting their asthma medication after identification of their pregnancy reported no influence on their asthma symptoms, while the other 5 (63%) reported worsening of asthma symptoms after adjustment. In the end, 22 (44%) women adjusted their asthma medication before or during pregnancy because of possible risks of their asthma medication for their infant and this was advised by their physician for 18 of them; 4 women stopped taking their controller asthma medication at their own initiative, but kept using their short-acting bronchodilator as needed. For 12 (55%) respondents, the adjustment of medication led to a worsening of asthma symptoms while for the other 10 the adjustment had no influence on asthma symptoms.

Table 3 shows the asthma medication adjustments mentioned by the responding women advised by their physician because of possible risks for the infant. The medications stopped or changed most often were the combination preparations consisting of an inhalation corticosteroid together with a long-acting bronchodilator.

Table 3: asthma medication stopped or changed advised by physician (N = 18)

Medication stopped:		n
combination *		3
formoterol		1
fluticasone		1
Medication changed:	changed to:	n
combination *	beclometasone	5
combination *	budesonide	4
fluticasone	beclometasone	1
budesonide	beclometasone	1
montelukast	budesonide	1
unknown	unknown	1

* inhalation corticosteroid and long-acting bronchodilator

Participants were asked what they perceived as best for the health of their infant: little symptoms due to medication or the avoidance of particular medications. A small majority of women (n=27, 55%) preferred little symptoms due to medication for the health of their infant.

Remarkably, of all women adjusting their medication after recommendation of their physician because of probable risks for the infant (n=18), 13 (72%) preferred little symptoms due to medication over avoiding particular medications. Ten women (20%) thought that mild dyspnoea could be harmful for the infant, while 38 (76%) and 40 (80%) thought this could be the case for an asthma exacerbation and asthma medication respectively. Sixteen women (32%) disagreed with the proposition "My physician provided me with clear information about the risks of my asthma and my asthma medication for my infant", but only one of them had actually discussed her asthma in relation to her pregnancy wish before she was pregnant. Twenty-three women (46%) looked for information themselves and 16 women (32%) thought that the information they got or found was contradictory. Almost half of the women (n=23, 46%) had had worries about the right choices regarding their asthma medications for the health of their infant, irrespective of whether the pregnancy wish was discussed with a physician in case of a planned pregnancy.

Discussion

Literature suggests that many women stop their asthma medication, often even without consulting a physician [9,13,14]. In our study the physician has a substantial role, only 4 women adjusted their asthma medication out of concern for the health of the infant at their own initiative. In spite of guidelines advising the opposite, our study shows that still many women are advised by their physician to stop or change their current asthma medication when planning a pregnancy or after pregnancy is identified, leading to an increase in asthma symptoms for more than half of them. Generally, relatively new medications containing a long-acting bronchodilator for maintenance of more severe asthma were stopped or changed to the older plain inhalation corticosteroids beclometasone or budesonide with substantial risk of the asthma getting less well controlled with consequent risks for the infant. This is in line with our earlier study on prescribed asthma medication before and during pregnancy in which almost 30% of women with asthma stopped their controller therapy, especially long acting bronchodilators [8]. Prior to pregnancy, the asthma was well controlled according to 92% of respondents, but when completing the survey during pregnancy, almost a quarter of women scored moderate or poor on asthma control.

Of all women adjusting their asthma medication on advice of their physician because of the health of their infant, more than 70% would prefer well-controlled asthma over avoiding particular medication after all and over 50% experienced a worsening of asthma symptoms after the adjustment of their medication.

Women seem to follow the advice of their physician, maybe even despite their own preferences, stressing the importance of the health care provider in asthma care during pregnancy even more. Women might also not perceive their asthma symptoms as severe enough to be a risk for their infant, since Boulet has shown that in the general asthma population, people underestimate the severity and control of their asthma [15]. Physicians appear to know and explain the established risks of poorly controlled asthma over the risks of asthma medication, but apparently knowledge and practice are inconsistent. The initial reserve against the use of newer asthma medications, especially long-acting bronchodilators, because of limited research that inconclusively proves them to be save is very persistent.

Pregnant women are very cautious about taking medication during pregnancy. They want to be sure that a medication is safe and needed before they are willing to take it [14,16]. Therefore, clear communication about the possible risks is of uttermost importance. Almost half of all pregnant women responding to our survey indicated to have had worries about the right choices regarding their asthma medications during pregnancy and there was no difference between women that planned their pregnancy and discussed their pregnancy wish in relation to their asthma or women who did not discuss this beforehand. More than 60% of the women that planned their pregnancy did not discuss their asthma management before pregnancy anyway. This is consistent with data from literature showing that worries about the safety of asthma medication during pregnancy are often not discussed with a health care provider [15,17]. Ideally, women planning a pregnancy should discuss their asthma and pregnancy wish with their physician and express their worries. The physician can give reassurance about the relative safety of their current medication compared to the established risks of poorly controlled asthma. Therefore, we would have expected women discussing their asthma treatment before pregnancy to be more prone to maintain their medication the way it was than women not discussing their pregnancy wish, but since almost two-third adjusted their medication accordingly, the opposite seems the case. Still pregnant woman highly value the information and advice of their health care provider. Almost all women discussing their pregnancy wish with their doctor were of the opinion that they had been given clear information from their physician about the risks of their asthma and their asthma medication for their infant. Earlier research showed that pregnant women indicated that when a health care provider would urge them to continue their medication in favour of their child, many would choose to do so [17] and women are more likely to continue adequate asthma medication in pregnancy when they are sufficiently informed about the risks of poorly controlled asthma and the benefits of optimal asthma treatment [14].

Our study endorses the problem of apparent communication about the potential fetotoxic risks of maternal conditions and medication.

Generally, almost one third of the respondents indicated that the information they got or found was inconsistent. Earlier research also suggests that women often feel they do not get clear information about asthma during pregnancy and many women like more education and support in order to maintain a better control of the asthma in pregnancy [14,18,19].

Since the thalidomide disaster however, in which more than 10,000 children were affected with congenital malformations after worldwide distribution of the drug for the treatment of morning sickness in pregnant women [20], health care providers might be reluctant to indicate a medication as safe to use during pregnancy. Lim et al show that although general practitioners generally had a good understanding of the safety of asthma medications during pregnancy, almost 25% would adjust controller asthma medication during pregnancy, in spite of good asthma control [21].

Literature also showed that pregnant women as well as health care providers are inclined to overestimate teratogenic risk, even after being assured that a certain medication is safe to take in pregnancy [22-24]. Concerning this, the way a risk-profile of a certain medication is communicated is of great importance. Risks and benefits are hard to weigh and value in order to make a decision and perception of risk is influenced by many additional factors [25]. This is complicated by the fact that epidemiological studies often report relative risks rather than absolute risks. A doubled risk of a particular birth defect after exposure to a certain medication sounds frightening, while the absolute risks of the birth defect are still very small [25]. Therefore, pregnant women could be provided with absolute risks estimations of their asthma medication rather than relative ones and the evident fetal risks of poorly controlled asthma should be emphasized. Positive framing might add to correct risk-assessment. Presenting the changes of giving birth to a healthy infant instead of the probability of giving birth to a malformed child lowers risk perception and might increase continuation of medication [26]. Additional research should be conducted to establish the safety of newer asthma controller medication in order to be able to provide physicians and patient with clear and correct information.

Our web-based survey recruited a highly diverse sample of asthmatic pregnant women. Younger, highly educated pregnant women tended to be overrepresented, however, but subjects responding to other modes of data collection often do as well [27]. Since Internet use has increased to 99% of all Dutch individuals using the Internet in the last 3 months in 2011 [28], selection bias due to limited access to the Internet is hardly to be expected. Selection based on disease severity might have occurred for the participants responding via open recruitment on the website of The Lung Foundation Netherlands. Women experiencing more asthma symptoms or having more concerns about the consequences of their condition or medication on the unborn child might be searching for information on asthma during pregnancy more often.

In conclusion:

The counselling of women with asthma who want to become pregnant can be improved. Many women have their worries about possible fetal risks of their asthma medication and information is often regarded to be contradictory. However, the majority of women that want to get pregnant do not discuss their asthma management with their physician. Yet they perceive a lack of support and guidance, indicating the need for properly worded information about asthma management in pregnancy to asthmatic fertile women irrespective of a current pregnancy wish. Women that want to get pregnant should be asked about fears and concerns about the safety of their medication for their infant to be able to receive adequate counseling explaining the importance of adequate asthma control and the relative safety of asthma medication over poorly controlled asthma [15]. Since women that do consult their physician often are advised to leave or change their asthma medication, often leading to a decrease of asthma control, healthcare providers need to be educated about the practical implementation of their knowledge about the importance of adequate asthma control in pregnancy [24].

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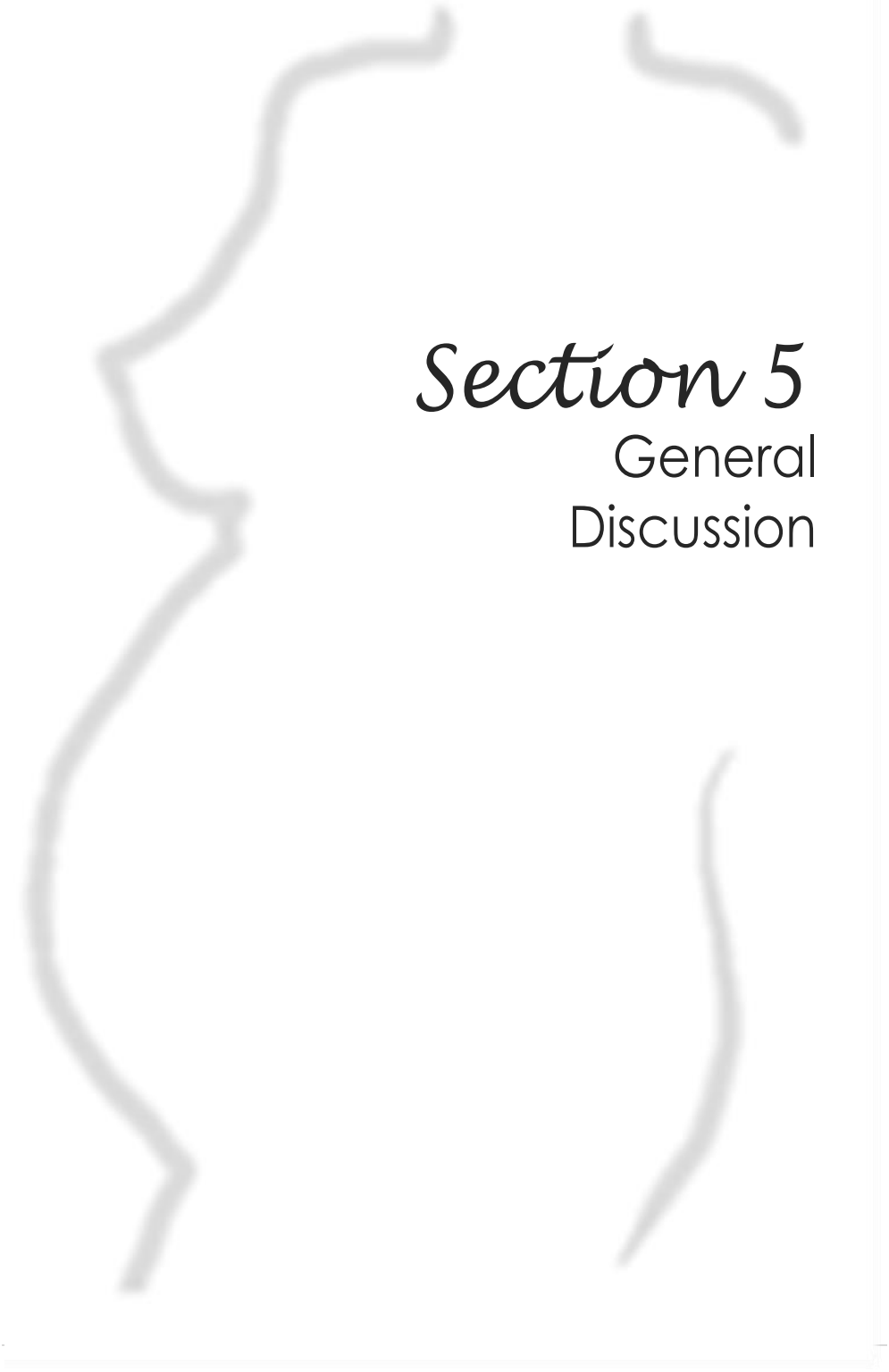

Section 5

General Discussion

Observational epidemiologic research is very important in establishing the safety and risks of medication use and lifestyle factors in pregnancy. Data for different kind of observational studies can be obtained in various ways. In this thesis we evaluated different modes of data collection that can be used.

Data collection and response rate

Direct data collection via pen-and-paper questionnaires from exposed subjects or subjects with a certain medical condition or the outcome under study themselves, has been one of the traditional methods of gathering the required data for observational epidemiological research. In the studies shown in Chapter 2.1 and 2.2 a traditional once-only questionnaire was administered to pregnant women attending their midwife or gynaecologist to collect information about their folic acid supplementation before and during pregnancy. Recent literature suggests an overall decline in recruitment rates for epidemiological studies over the last decades [1]. Yet in our folic acid study from 2009 (Chapter 2.1), recruitment rate was very high. All questionnaires were handed out and only a few women refused to fill out the questionnaire, leading to a recruitment rate of 94%, which is even higher than in the earlier monitors starting in 1995 where recruitment rates varied from 75 to 90% [2]. However for the folic acid monitor carried out in 2014 in the Northern Netherlands (Chapter 2.2), response rate dropped considerably. From all questionnaires that were sent to the participating practices, 49.7% was completed and returned. Follow-up calls to the participating practices to inform about the study progress might have been less frequent, but the only methodological difference between the 2014 survey and the previous ones was that in the earlier surveys participating midwiferies and gynaecological departments were provided with a financial incentive for every completed questionnaire that was returned. For the 2014 survey there was no available budget for incentives. Although the majority of practices that were approached agreed with participation, the absence of the incentive had a direct impact on the efforts of the health care workers involved and as a consequence on the number of returned questionnaires. Literature had already demonstrated the stimulating effect of incentives on response rates when approaching possible participants including physicians [3,4].

Another point that was raised by the participating health care workers that might have influenced response rate was the vast amount of research conducted in the field. Midwiferies and gynaecologists were asked to cooperate in a lot of research and they were reluctant to ask consulting pregnant women to participate in yet another study and provoke irritation. It has been shown that there has been an increase in research studies over the last decades, and the epidemiologic studies conducted have become increasingly demanding and complicated [1].

Maybe we ask too much of our target population, creating overall reluctance to attend epidemiological research that might contribute to the declining response rates observed.

Web-based questionnaires in relation to sample size

One of the methods to meet the declining response rates in traditionally conducted epidemiological surveys is thought to be the administration of a web-based questionnaire [5,6,7]. Generally, response rates for web-based questionnaires have been lower than for mailed questionnaires [5,8]. Furthermore, as shown in Chapter 4.1, where we investigated available literature on the use of web-based surveys examining a pregnancy-related topic, for web-based surveys using open recruitment via the Internet, it is usually not possible to determine response rate. The actual size of the target population and the number of individuals than can be reached is mostly unknown. Yet the feasibility to build a fairly simple web site and to reach your target population online might render the possibility to collect a relatively large number of respondents at little expense [7].

In our review of the use of web-based surveys in pregnant or recently pregnant women examining a pregnancy-related topic (Chapter 4.1) the number of participants recruited per day varied widely from 0.4 to 663 participants per day. Recruitment numbers highly depend on the target population and the recruitment methods used [9]. Studies included in our review investigated very different topics with relating target populations and they used very different recruitment strategies.

For the PROTECT pregnancy study, (Chapter 4.2), a European prospective study run in Denmark, The Netherlands, Poland and the UK on new methods for data collection, where pregnant women were asked to provide information about their health, lifestyle factors and medication use via the Internet, the number of participants fell short of expectations from the start. We aimed to recruit 1200 pregnant women per participating country (a total of 4800) for the Internet survey, but after increasing our efforts and our recruitment budget we finally were able to recruit 2065 women that completed the baseline questionnaire. The limited recruitment period compared to what was originally planned also played a role in not reaching our recruitment target.

For our study on asthma perception during pregnancy (Chapter 4.3), we also targeted pregnant women with asthma via the Internet. The call for participation was available online during a period of more than a year and resulted in only 15 respondents starting the questionnaire of whom 11 completed it. The asthma perception study might have been able to recruit more participants if the recruitment strategies were elaborated.

The only announcement of the study was on the website of The Lung Foundation Netherlands (Het Longfonds), the Dutch patients' association for people with chronic lung disease. Calls could have been made on other websites relating to asthma and/or pregnancy as well or pregnant women with asthma could have been targeted at discussion platforms or via social media for example.

The overall design of the study website and the questionnaire used is of great importance as well [10]. Communicating information about the purpose and the study itself should be plain and clear [11]. For the PROTECT pregnancy study we aimed to be as complete as possible when informing potential participants about the study purpose and design since respondents have to be able to give a fully informed consent. People are more willing to respond to a survey when it shows authority [10,11], but one has to be careful not to scare people of by using language that is difficult to understand, especially for the lower educated. Another pitfall is to address every possible small risk participation entails, for example with privacy, and stress all actions taken to minimize them which might deter possible participants instead of providing reassurance.

Collecting a large sample of web-based survey respondents via the Internet is very well possible, but there is no guarantee for success. For the recruitment of a sufficient sample of participants the investigator needs a lot of creativity and Internet-literacy and it takes a lot of effort and coordination to build an appealing website and roll out an adequate recruitment strategy [11]. For a study as large as the PROTECT pregnancy study an expert in the areas related to the target population and website design and recruitment might have saved us a lot of problems and costs.

The size of a sample is not everything though. Selection bias lays wait when respondents differ from non-responders [5,9] and as stated in the introduction, selectivity has been seen as one of the major pitfalls for Internet samples for epidemiologic research. Chapter 4.2 shows that in our PROTECT pregnancy study participants differed substantially at several points from the target population. But this is not a potential problem solely for Internet surveys. The evaluation of the representativeness of potential controls recruited via midwiferies where data was collected by pen-and-paper questionnaires (Chapter 2.3) showed selectivity of the sample as well. Literature confirms that respondents attending a web-based survey are comparable to the ones participating in traditional survey methods [5,12]. Furthermore, the Internet might bring opportunities to circulate the announcement of a survey on a large scale, but literature shows that people recruited via the Internet to form a cohort had a higher rate of lost to follow-up than people recruited offline [13]. The PROTECT pregnancy study showed a high drop-out rate as well, with only 30% of participants with a due date within the study period to be followed throughout pregnancy. When respondents that are lost to follow up differ from people that retain in respect to relevant exposures, selection bias will increase.

Indirect data collection

The third section of this thesis discussed four studies where data was used from a pharmacy prescription database and a birth defect registry. These studies all looked at the use of certain medication during pregnancy, either to assess prevalence of medication use (asthma medication in pregnancy in Chapter 3.1), associations between medication use and certain outcome in the offspring (high-dose folic acid during pregnancy and asthma symptoms in the offspring in Chapter 3.2 and folic acid antagonists during pregnancy and folic acid sensitive birth defects in Chapter 3.3) or the feasibility to combine both databases to generate signals of teratogenic risk of drugs for further research (chapter 3.4). Chapter 3.1 shows that pharmacy prescription data are very valuable for drug-utilization studies. Despite obvious limitations like the lack of information on actual use, indication for prescription and maternal characteristics and possible missing data, we gained important understanding of the continuation of asthma medication around pregnancy. The demonstrated patterns of refraining or changing established asthma medication when planning a pregnancy or after pregnancy confirmation, were confirmed by our asthma perception study (Chapter 4.3) where we used a completely different approach and asked pregnant women themselves about their asthma medication use and changes before and during pregnancy. These corresponding results show that pharmacy prescription data can be a good data source for epidemiological research, even when the dosing of the medication prescribed is not very uniform as is especially the case with inhalation medication where number of inhalations will be adapted to current asthma symptoms.

For epidemiological research investigating risk patterns for certain disease outcomes however, a pharmacy prescription database lacks outcome information and information on other maternal risk and possible confounders. One way to assess disease outcome using a pharmacy prescription database is to take medication use for the outcome under study as a proxy for that outcome as elaborated in Chapter 3.2. This method has been used for several outcomes in the offspring lately, like the use of laxatives and antidiarrheal medication as a proxy for constipation and diarrhoea respectively, drugs for pulmonary diseases as a proxy for disturbed respiratory tract development and the use of local steroids as a proxy for allergic diseases and shows to be very usable [14-16]. The associations found were adjusted for any possible confounders known, but since there is no information on other maternal and pregnancy characteristics, residual confounding cannot be excluded. Therefore it would be very helpful if a pharmacy dispending database like the IADB.nl could be linked to other databases like among others, the Stichting Perinatal Registration Nederland (PRN) [17] containing maternal data, pregnancy data and data on pregnancy outcome. A recent EUROmediCAT study showed that linkage of prescription databases to birth defect registries improve the quantity and quality of information on maternal medication use in pregnancy [18].

Using a birth defect registry for assessing possible relations between medication use in pregnancy and certain birth defects entails the challenge of finding an adequate control group. The signal detection study (chapter 3.4) showed that combination of data from a population based pharmacy prescription database with data from a birth defect registry can be used for signal detection. However, the method is not suitable for establishing possible relations, since case-group, pregnancies of children with a congenital malformation registered within the EUROCAT NNL database, and control-group, pregnancies detected in the IADB.nl database, are not comparable concerning data collection and composition. In chapter 3.3 malformed controls affected by a chromosomal or other genetic abnormality registered within the EUROCAT NNL database were used. Taking malformed controls from the same database guarantees consistent collection of data on maternal characteristics, exposures and pregnancy outcomes for both cases and controls. By only taking chromosomal and genetic disorders as controls, that have their origin before development of the fetus the chances of misclassification are very low and recall bias is avoided. Controversy remains though, because in the end, one cannot be complete sure that there is no association between the malformations in the control group and the drug under study, which would lead to an underestimation of the association studied [19,20].

Therefore we started a pilot to set up a database with information on pregnancies where the mother gave birth to a non-malformed baby. Results are shown in chapter 2.3. The Healthy Pregnant database turned out not to be representative for the general pregnant population in the northern part of the Netherlands though and numbers recruited were low. As the PROTECT pregnancy study also showed, it is very hard to compile a pregnancy cohort that is really population based and representative due to low response rates and definite differences between participating women and women not included in the pregnancy cohort.

Another challenge when performing risk assessment studies looking at birth defects, and especially birth defects that are rare is the problem of acquiring an adequate number of cases. When using the EUROCAT NNL database covering approximately 10% of all births in the Netherlands and containing more than 14,500 registered pregnancies and children with congenital anomalies [21]. Chapter 3.3 and 3.4 show that for the assessment of several associations between medication use and congenital malformations, numbers are too low. Even when a malformation is relatively common like heart defects (around 8 per 1000), low prevalence of medication use might lead to too few exposed cases for an accurate risk assessment. The EUROCAT network includes 43 registries of congenital anomalies in 23 countries, covering 29% of all births in Europe. Combining data from all these birth defect registries will largely increase statistical power to demonstrate teratogenic effects of medications [22].

The estimated average of major congenital malformations in the general population is approximately 3% [23,24].

In the PROTECT pregnancy study including 464 women that were followed until childbirth, only about 14 children with a major birth defect are to be expected. This implies that for a database like the PROTECT pregnancy study to be useful for the assessment of relations between certain exposures and particular congenital malformations, the study needs to be extensively expanded involving corresponding effort and costs. The question arises whether a big enough online pregnancy cohort like this will be feasible.

Folic acid supplementation

Finally, I would like to refer to the other focal points mentioned in the general introduction, starting with folic acid supplementation before and during pregnancy. The surveys addressing folic acid use before and during pregnancy from 2009 and 2014 presented in chapter 2.1 and 2.2 show that the recommended use of a folic acid supplement containing at least 400µg from 4 weeks before conception until 8 weeks thereafter has stabilized a at a level just over 50% in the Northern Netherlands, despite initial declining of knowledge about the recommended period. Yet there is a lot to gain in the prevention of NTDs, since the other half of all pregnant women do not use folic acid as recommended. Education about the preventive effects on NTDs and adequate use of folic acid supplementation should find unabated progress and new initiatives might be able to increase recommended folic acid use. Levels of 100% will never be reached, there will always be unplanned pregnancies or women that are uninformed, indifferent or unconvinced about the benefits of folic acid supplementation. There is an on-going debate about the benefits and drawbacks of fortification of foods (mostly staple foods like grain products) with folic acid [25,26]. In the Netherlands and other EU countries there is no mandatory fortification of foods with folic acid unlike in the USA, Canada and other countries. In the US mandatory food fortification with folic acid has thought to have prevented a substantial number of NTDs so far [27]. Chapter 3.2, where we conclude that high dose folic acid use during pregnancy might increase the risk of childhood asthma pleads for some restraint though in the case of unlimited folic acid supplementation or fortification. Yet in spite of plurality of research, a lot is still unclear about the benefits and possible drawbacks of folic acid supplementation.

Asthma medication in pregnancy

Chapter 3.1 as well as Chapter 4.3 investigating the use of asthma medication in pregnancy and women's perceptions about their asthma and asthma treatment, show that in the field of asthma management during pregnancy there is still a lot to gain.

Latest guidelines are often not being followed and although there is sufficient knowledge about the relative safety of asthma medication over poorly controlled asthma, reluctance among physicians to maintain newer asthma medication throughout pregnancy is persistent. Training of health care workers involved in asthma treatment should stress the importance of adequate asthma control during pregnancy for the health of mother and child and should address possible residual concerns about medication safety to be able to provide reassurance.

In summary

This thesis show that the several methods of data collection on risk factors in pregnancy, for observational epidemiological research all have their pros and cons, including those using new methodology like collecting data via the Internet. The use of a questionnaire enables the researcher to collect sufficient data on all variables needed including possible confounding factors identified beforehand. When using traditional recruitment methods like mail or telephone, source population is known and recruitment rates can be calculated. Follow-up often is higher than with Internet samples. Internet recruitment on the other hand renders the possibility of reaching a broad target population. Technology has evolved very fast over the last decade. Especially young people are permanently connected to the Internet using their smartphones and their social lives takes place on discussion platforms and social media to a great extent. With millions of webpages with information on every topic imaginable, the Internet is the first place where people will start to look when searching for information. Therefore, Internet might be a better way to approach women in fertile age. Sufficient knowledge is of great importance though, because numbers recruited vary a lot depending on target population, recruitment strategy and design of the study-website. Prospective direct data collection provides information about exposure that is more complete than information collected retrospectively and avoids recall bias. Databases capturing existent medical data like a pharmacy prescription database have the advantage that population based data is available for a large number of subjects. Linkage of different kind of datasets can be very valuable in contributing to a dataset for risk-assessment studies containing data that is as valid and complete as possible.

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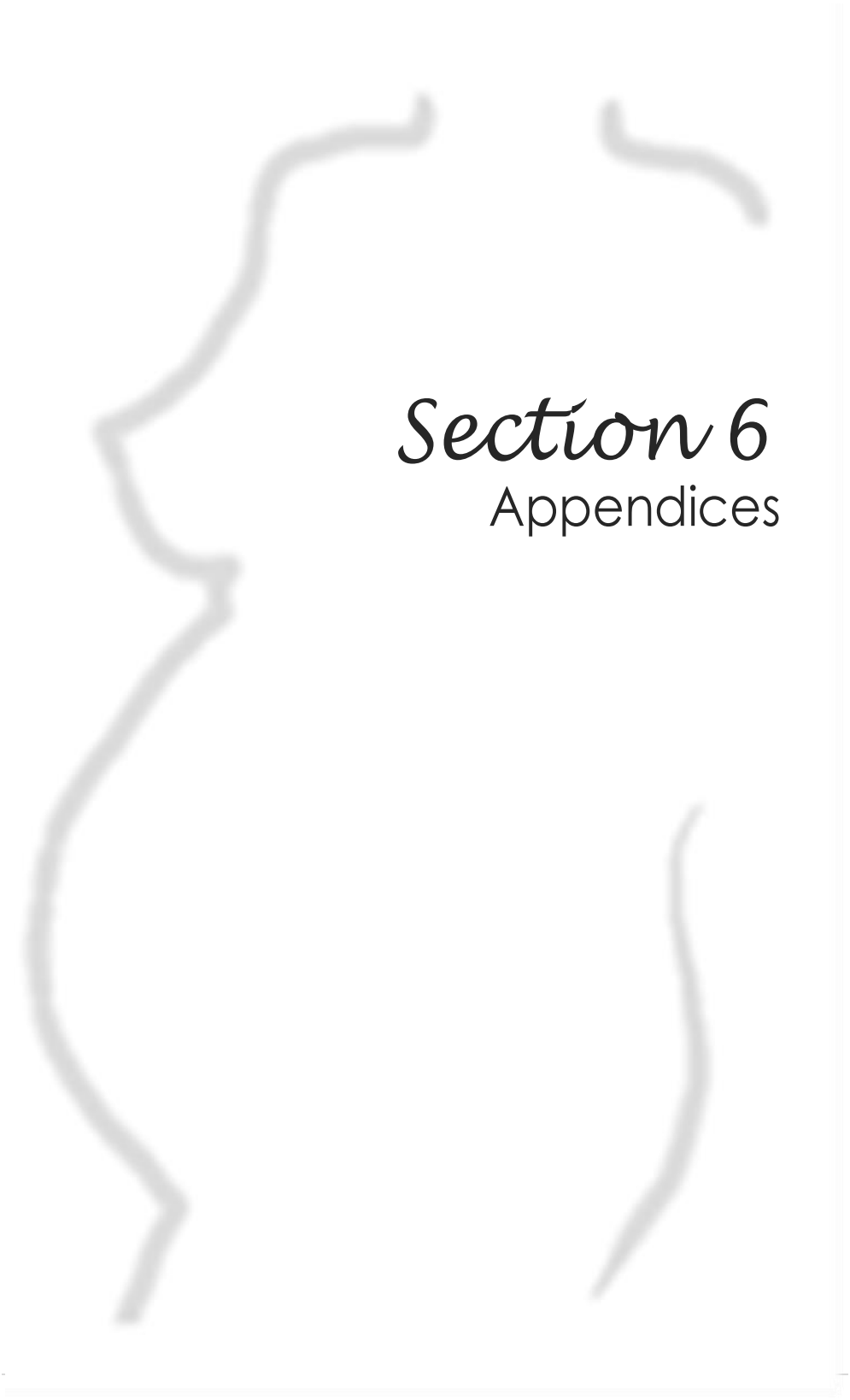

Section 6
Appendices

Appendix 1: PROTECT Pregnancy: An Exploratory Study of Self-Reported Medication Use in Pregnant Women.

Work Package 4: New Tools for Data Collection from Consumers

Background and Rationale

The use of therapeutic medication during pregnancy, whilst in many cases essential for the health of the mother, causes concern regarding the potential for deleterious effects on the foetus. Indeed, medicine use in pregnancy can be related to a variety of adverse outcomes, including not only congenital malformations, but also preterm birth, intrauterine growth restriction, spontaneous abortion, late foetal death, neonatal death, or developmental disabilities (behavioural, neurological, motor, intellectual or sensory) that only become apparent in later infancy or childhood.

A priori knowledge of the effects of many medicines taken during pregnancy is often limited. Consequently, many drugs are contraindicated or have special warnings because their safety during pregnancy has not been studied sufficiently. Some drugs can be avoided during pregnancy; however, medications for chronic diseases such as diabetes, epilepsy, asthma, and rheumatic diseases may need to be continued during pregnancy since these conditions, left untreated, can be both detrimental to the mother and the foetus.

Medication use in pregnancy cannot always be avoided, therefore, it is critical to collect information on drug exposure in relation to gestational age to answer questions on whether a medicine may harm the foetus and, if it does, on the developmental stage when the foetus is vulnerable to the effects of the drug.

For all study designs, collection of proper information about exposure and outcome is essential. In addition to medication, it is also important to collect data on lifestyle factors including alcohol consumption, smoking and the use of drugs of abuse, all of which have been associated with adverse pregnancy outcomes. Ideally, to avoid bias, complete exposure to medications and risk factor information needs to be collected prospectively at frequent intervals and before the pregnancy outcome is known [1-4].

Need for New Methods to collect information from consumers

Several existing data sources can be used to obtain information on medication use, lifestyle factors and pregnancy outcome to study possible risk factors in pregnancy, like electronic healthcare records, pregnancy registries and registries of congenital malformations.

The majority of these data sources collect their data on drug exposure during pregnancy either from health care professionals, through direct patient questioning by an interviewer (frequently a midwife) or have utilised prescription or dispensing records. Using researchers to collect information is time consuming and expensive, and can only be performed at relatively infrequent times during the pregnancy, which may lead to lost information [3]. In addition, women may be reluctant to report accurate information about lifestyle behaviours already identified as being potentially harmful to a foetus, or which are in themselves illegal, in a face-to-face interaction. There is some evidence that using the Internet may overcome these issues [5].

This study will explore and assess whether women in participating EU countries are willing to provide information via the Internet to enable prospective collection of medication exposure data and information about other life style factors during pregnancy. This study will also use an alternative method of data capture – an interactive voice response system (IVRS) - to capture data and will compare the demographics and attributes of the two populations.

Objective

Assess the extent to which data collected directly from pregnant women via the Internet and IVRS provides information on medication use and other potential risk factors throughout pregnancy and is suitable for research purposes.

Research Question

Is the quality and quantity of information collected directly from pregnant women without intervention of health care professionals suitable for research?

This will be evaluated in the following ways and sub-analysed by country and by method of data collection (unless otherwise specified):

- Demographic characteristics and health status of pregnant women at study entry
- How consistently and for how long pregnant women recruited via internet will provide the data requested.
- For prescription drugs, evaluate the usage, accuracy and completeness of self-reported prescription drug use by comparing the responses with data from other sources (pharmacy data bases and electronic health records) in countries where such resources exist, or with national data.
- For non-prescription medications, describe the use of over-the-counter products, as well as homeopathic and herbal medication use in pregnancy.
- Where possible validate pregnancy outcomes.

- Compare whether the frequency of data collection affects the completeness and accuracy in women recruited via Internet.
- Assess the extent to which women will provide "sensitive" information about lifestyle and other risk factors for congenital effects
- Loss to follow up and reason for discontinuation in women recruited via Internet

Finally, transferability to other patient populations and other countries will be considered.

Methods

Study Design

This is a prospective, non-interventional, descriptive study of pregnant women who volunteer to provide information about their medication use and relevant life style factors on a periodic basis throughout their pregnancy. Data will be collected directly from eligible subjects through the Internet or via interactive voice response systems (IVRS) in the four participating countries: Denmark, the Netherlands, Poland and the United Kingdom(UK). Three of the four countries (Denmark, the Netherlands, and the UK) have systems in place for recording prescription data, either on a national basis (Denmark), regional (the Netherlands) or as part of automated data collection from specific practices (UK: THIN). The data collected from the study subjects will be compared with this information. Aggregated, anonymised data from the study population will be compared with data collected from these systems on either a regional or national basis depending upon data availability. With the explicit consent of the study subjects, linkage at the individual level will be explored to assess the congruity and differences between the electronic data and that collected directly from the study subjects.

Choice of data entry and follow up

Women, who choose to enrol, will be given a choice of entering data via a secure website or via IVRS and keypad data entry. Once the IVRS limit is reached, only women who are willing to provide data via the Internet will continue to be recruited. Women who chose to provide data by Internet will be able to choose whether they provide data every two or four weeks. Those who chose to provide data by the IVRS will only provide baseline and outcome data to the study. Reminders as to when data provision is required are sent by e-mail, text message or automated phone call, depending on the participant's choice.

Duration of follow up

Ideally women are followed from when they self-enrol in the study until the end of their pregnancy from whatever cause, unless the pregnancy ends after study completion. Information will be collected at baseline and via Internet every 2-4 weeks until the end of the pregnancy or study closure whichever comes first. Information on pregnancy outcome will be requested at the time the pregnancy ends, and a reminder will be sent monthly for up to 3 months. Data on pregnancy outcome will also be sought through from women who enrolled through IVRS. Since data are entered directly by the women, continuation in the study is an active choice and women may cease participation in the study at any time.

Population and subject recruitment:

Study subjects will be recruited from four countries: Denmark, Poland, the Netherlands and the UK. Data will be collected in the predominant national language in each of the four countries. Informed Consent will be obtained from all subjects prior to study participation in accordance with local requirements.

Subjects will be recruited for study participation through informational materials and methods such as (but not limited to):

- Leaflets located primarily at pharmacies or midwives' clinics).
- Advertisements on selected healthcare-related Internet sites.
- Advertorials in selected magazines or journals
- Advertisement bulletins on Internet pregnancy forum websites and social network websites.

Data Collection

Data will be collected on use of prescription and non-prescription medications, as well as on use of herbals and homeopathic medications. Questionnaires were developed from a review of best practice documents (i.e. questionnaires used in other long-term pregnancy studies) and with the participation of a patient organisation (IAPO). More information will be collected from women who provide their response over the Internet than by phone, in order to utilize the full capacity of Internet- based data collection.

Registry baseline data elements include data such as the following:

- Demographics information.
- Information about co-morbid diseases/conditions and corresponding medication treatment.
- Pregnancy Information, such as date of Last Menstrual Period (LMP), and previous pregnancy information.

- Current medication use, including prescription, over the counter (OTC), herbal/homeopathic medications and whether any medications taken came from other people (shared medications).
- Other Risk Factors (i.e., smoking, use of recreational drugs).
- Follow up questionnaires will be available for those who chose to provide data through the secure website.

The variables to be ascertained during follow-up include:

- Changes in co-morbidities from baseline/not yet recorded and corresponding medication treatment.
- Changes in prescription medications.
- In addition to the above, participants entering information via the Web tool will record details related to changes in over the counter (OTC) and herbal/ homeopathic medications.

The variables to be ascertained at pregnancy outcome, registry close out or discontinuation include:

- Changes from baseline for co-morbidities for which medications are taken (not yet recorded).
- Pregnancy outcome information, such as defects at birth; birth weight, premature delivery, etc.
- Evaluation of the program, in terms of assessing the ease of data collection and any other feedback provided by the study participant.

Statistical Analysis

A detailed statistical analysis plan addresses the points below.

1. To compare characteristics of IVRS patients with web patients recruited at the same time (i.e. only compare women who had a choice of data entry)
2. To compare data between countries for (3) – (15).
3. To describe demographics of women who choose each method of data entry
4. To compare demographics of women recruited with those recorded on healthcare databases: DK – national data, NL local data, UK THIN data.
5. To describe data on time of pregnancy at recruitment.
6. To describe the length of time and the frequency that participants will provide data. To compare those willing to provide data monthly versus fortnightly. To apply missing data analysis where necessary.
7. To classify and determine the stage of foetal development to be used for analysis
8. To descriptively compare prescription drugs in cohort by stage of foetal development.
9. To describe use of non-prescription, homeopathic, herbal medications by stage of foetal development

10. To describe how many people could and could not be individually matched for data linkage in the UK. In Denmark, all women should be linked to the Register of Medicinal Product Statistics
11. To compare data quality from healthcare databases on medications use to participants-reported data, where linkage is available. To undertake paired analysis and/or describe the differences where possible. This applies to both prescription-only and non-prescription medications.
12. To describe use and willingness to provide data on illegal drugs, smoking alcohol etc., and to compare them against medical records where available.
13. To describe the outcomes of pregnancy.
14. To describe risk factors for malformations.
15. Where data permits, validation of outcome data by comparing the data with external data sources such as malformation registries.
16. If the quality of data permits, to compare actual vs. probabilistic linkage of participants-reported data to healthcare databases. The algorithm for the linkage will also be discussed.
17. To describe ease of use of systems, to perform SWOT analysis, and to discuss the potential for transferability to other patient populations.

Sponsorship

The study will be conducted as part of the PROTECT project (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium, http://www.imi-protect.eu) which receives funding from the European Union's Seventh Framework Programme (FP7/2007-2013) for the Innovative Medicine Initiative (www.imi.europa.eu; Grant Agreement n° 115004). Some of the entities participating in PROTECT and the conduct of the present study are EFPIA (European Federation of Pharmaceutical Industries and Association) member companies and costs related to their part in the research will be carried by the respective company as in-kind contribution or as direct financial contribution to one of the non-EFPIA partners under the IMI JU scheme.

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Appendix 2: Supplementary tables Chapter 3.2.

Supplementary Table 1: asthma medication filled by children recorded in the IADB.nl pregnancy database.

ATC-code	Asthma medication	Number of children (ntot = 11780)	%
	Short-acting bronchodilators		
R03AC02	salbutamol	9923	84,24
R03AC03	terbutaline	416	3,53
R03BB01	ipatropium	634	5,38
R03CA02	ephedrine	1	0,01
R03CC02	salbutamol oral	430	3,65
R03CC03	terbutaline oral	96	0,81
	Inhalation corticosteroids		
R03BA01	beclometasone	1645	13,96
R03BA02	budesonide	946	8,03
R03BA05	fluticasone	5187	44,03
R03BA08	ciclesonide	8	0,07
	Long-acting bronchodilators		
R03AC04	fenoterol	1	0,01
R03AC12	salmeterol	97	0,82
R03AC13	formoterol	52	0,44
R03BB04	tiotropium	2	0,02
	Combination preparations:		
R03AK03	fenoterol/ipatropium	111	0,94
R03AK04	salbutamol/ipatropium	186	1,58
R03AK06	salmeterol/fluticasone	431	3,66
R03AK07	formoterol/budesonide	145	1,23
	Other asthma medication		
R03BC01	cromoclicic acid	20	0,17
R03BC03	nedrocromil	1	0,01
R03BX	fenspiride	1	0,01
R03DA04	theophylline	3	0,03
R03DC03	montelukast	256	2,17

Supplementary Table 2: ATC-codes used to define possible confounding factors.

Medication	ATC-code
Asthma medication	R03
Antiepileptic medication	N03A
Sulphonamides and trimethoprim	J01A
Antihypertensives	C02, C03, C07, C08, C09
Antidepressives	N06A
Antidiabetics	A10
Benzodiazepines	N03AE, N05BA, N05CD,N05CF

Supplementary Table 3: Stratified analyses for the association between dispensed high dose folic acid and asthma medication for the child.

Stratification on maternal age					
30 years of age and younger	Adjusted and clustered association*		*over 30 years of age*	Adjusted and clustered association*	
Outcome	IRR#	95% CI		IRR#	95% CI
Any asthma medication	1.17	0.99-1.37		0.95	0.80-1.10
Recurrent asthma medication	1.34	1.11-1.61		1.01	0.84-1.21
Any ICS§	1.42	1.16-1.75		1.07	0.88-1.31
Recurrent ICS§	1.47	1.16-1.87		1.12	0.89-1.40
Stratification on maternal asthma medication					
maternal asthma medication	Adjusted and clustered association**		*no maternal asthma medication*	Adjusted and clustered association**	
Outcome	IRR#	95% CI		IRR#	95% CI
Any asthma medication	1.11	0.81-1.53		1.02	0.91-1.15
Recurrent asthma medication	1.14	0.80-1.64		1.15	1.00-1.32
Any ICS§	1.43	0.97-2.11		1.20	1.03-1.39
Recurrent ICS§	1.22	0.78-1.91		1.27	1.07-1.51
Stratification on maternal iron					
maternal iron during pregnancy	Adjusted and clustered association***		*no maternal iron during pregnancy*	Adjusted and clustered association***	
Outcome	IRR#	95% CI		IRR#	95% CI
Any asthma medication	1.14	1.00-1.30		1.11	0.87-1.42
Recurrent asthma medication	1.13	0.97-1.32		1.39	1.05-1.84
Any ICS§	1.20	1.02-1.42		1.48	1.10-2.01
Recurrent ICS§	1.18	0.98-1.43		1.73	1.23-2.42

* Adjusted for: dispension of benzodiazepines during pregnancy and maternal dispension of asthma medication.

** Adjusted for: maternal age and dispension of benzodiazepines during pregnancy.

** Adjusted for: maternal age, dispension of benzodiazepines during pregnancy and maternal dispension of asthma medication.

Incidence Rate Ratio

§ Inhalation corticosteroids

Appendix 3: Malformations that are coded within the malformation groups studied in Chapter 3.4. *

Malformations of the nervous system (neural tube defects):
- Anencephalus and similar
- Encephalocele, exclude if associated with anenephalus
- Spina Bifida
- Hydrocephalus but exclude hydranencephaly or associated with NTD
- Microcephaly but exclude if associated with NTD

Congenital heart defects (Exclude isolated PDA with GA <37 weeks):
- Arhinencephaly / holoprosencephaly
- Common arterial truncus
- Transposition of great vessels
- Single ventricle
- Tetralogy of Fallot
- VSD
- ASD
- AVSD
- Triscuspid atresia and stenosis
- Ebstein's anomaly
- Pulmonary valve stenosis
- Pulmonary valve atresia
- Aortic valve atresia/stenosis
- Hypoplastic left heart
- Hypolastic right heart
- Coarctation of aorta
- Total anomalous pulm venous return
- PDA as only CHD in term infants (GA +37 weeks); Livebirths only

Oro-facial clefts (Exclude if associated with holoprosencephaly or anencephaly subgroups):
- Cleft lip with or without cleft palate
- Cleft palate

Malformations of the digestive system
- Choanal atresia

Respiratory malformations
- Cystic adenomatous malf of lung

Malformations of the digestive system
- Oesophageal atresia with or without trachea-oesophageal fistula
- Duodenal atresia or stenosis but exclude if also annular pancreas
- Atresia or stenosis of other parts of small intestine
- Ano-rectal atresia and stenosis
- Hirschsprung's disease
- Atresia of bile ducts
- Annular pancreas
- Diaphragmatic hernia

Genital malformations
- Hypospadia
- Indeterminate sex

Malformations of the urinary tract
- Bilateral renal agenesis including Potter syndrome
- Renal Dysplasia
- Congenital hydronephrosis
- Bladder exstrophy and / or epispadia
- Posterior urethral valve and / or prune belly

Malformations of the musculo-skeletal system
- Skeletal dysplasias
- Craniosynostosis
- Congenital constriction bands /amniotic band

Malformations of the limbs
- Limb reduction
- Upper limb reduction
- Lower limb reduction
- Complete absence of a limb
- Club foot – talipes equinovarus
- Hip dislocation and / or dyspasia
- Polydactyly
- Syndactyly

* According to the EUROCAT guidelines: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3-Chapter-3.3-Jan13.pdf

Appendix 4: Malformations observed within cases exposed to the different drugs studied in Chapter 3.4.

valproic acid

heart anomalies RR 5.98 (2.66-13.44)

observed malformations:

- VSD [2x]
- VSD + aortic pulmonary window [1x]
- Fallot's [1x]
- tetralogy [1x]
- coarctation of aorta [1x]

anomalies of the central nervous system RR 15.05 (5.09-44.51)

observed malformations:

- spina bifida [2x]
- hydrops foetalis + mental retardation + epilepsia + congenital cataract [1x]

fluoxetine

anomalies of the digestive system RR 3.73 (1.23-11.32)

observed malformations:

- hypertrophic pyloric stenosis [3x]

citalopram

anomalies of the musculo-skeletal system RR 3.75 (1.26-11.14)

observed malformations:

- congenital deformities of the hip [2x]
- congenital deformities of the hip + unbalanced translocation [1x]

paroxetine

heart anomalies RR 2.03 (1.14-3.62)

observed malformations:

- VSD [4x]
- ASD [1x]
- coarcatation of aorta [2x]
- bicuspid aortic valve [1x]
- congenital pulmonary valve stenosis + cafe au lait spots [1x]
- VSD + clubfeet [1x]
- transposition + AVSD + dextroposition of the heart [1x]

methyldopa

anomalies of the digestive system RR 4.66 (1.54-14.06)

observed malformations:

- cloacal dysgenesia sequence [1x]
- hypertrophic pyloric stenosis [1x]
- atresia of oesophagus with tracheo-oesophageal fistula [1x]

genital anomalies RR 5.37 (1.78-16.22)

observed malformations:

- cloacal dysgenesia sequence [1x]
- hypospadias [2x]

urinary anomalies RR 5.46 (1.81-16.49)

observed malformations:

- cloacal dysgenesia [1x]
- vesico uretral reflux [2x]

Appendix 5: Detailed information about the studies included in the review shown in Chapter 4.1 investigating the use of web-based surveys examining a pregnancy-related topic.

Publications investigating a health-related topic:

Reference 11:

Topic: The perception of women of their asthma during pregnancy.
Population: Women who had asthma and were pregnant or had given birth within the previous three months.
Recruitment: An invitation letter was placed at the homepage of the investigators institution. A program was used that gets your website to be high-ranked with search engines. Period: 3 months. 300 responses, final sample: 166
Demographics: Mean age: 28.3 (SD 12.5); Country: US 88.6%, Canada: 4.8%, England 4.2%, Japan 1.8%, Germany 0.6%; 30.8% had a college degree or higher; First birth: 49.4%.

Reference 12:

Topic: Barriers and Benefits of a stop smoking course during pregnancy.
Population: Women who were pregnant and smoker or recent ex-smoker (<month).
Recruitment: Questionnaire posted on a smoking cessation website. Linked to website about smoking cessation and/or pregnancy. Period: Oct 2003 – Aug 2004 (11 months). 491 responses, 443 eligible.
Demographics: Mean age: 27.7 (SD 6.7); Country: North America or UK: 87.2%; Caucasian: 91.1%

Reference 13:

Topic: Differences between 2 groups of women trying to conceive, those who had not yet sought medical advice and those who had.
Population: Women trying for a child.
Recruitment: Questionnaire posted on a website targeted at couples just starting out in the process of trying for a child. (11 were contacted, 1 replied); Link placed at the top of every page. Period: 8 weeks. 498 responses, final sample: 426.
Demographics: Mean age: 28.6 (SD 3.2); Country: UK 48.1%, US: 38%; 75.1% was educated to college or university level.

Reference 14:

Topic: The psychosocial burden of HG (hyperemesis gravidarum).
Population: Women with HG (significant weight loss and debility requiring mediations and/or fluids).

Recruitment: A questionnaire on a HG website. Period: 2003-2005 (3 years). Final sample: 808.
Demographics: Mean age: 30.9 (SD: 5.0); Country: US 77.5%; 92.8% educated to college level; 28.6% being pregnant.

Reference 15:

Topic: Presentation and risk factors for PTSD after birth.
Recruitment: A link to the study website posted on relevant websites. 921 responses, final sample: 918.
Demographics: White: 97.5%; Highly educated: 82.4%; Primiparous: 65.2%.

Reference 16:

Topic: The perception of risk of well-known drugs and other exposures during pregnancy or breast-feeding.
Population: Women currently pregnant or having a child less than 5 years old.
Recruitment: Questionnaire on the University of Oslo's website for Internet surveys. An invitation was posted on 4 webpages for pregnant women and mothers. Period: 16 Sep – 25 Oct 2008 (5 weeks). 1821 responses, final sample: 866.
Demograpics: Mean age: 30 (17-45); Country: Norway; 68.7% higher educated; 38.4% first child.

Reference 17:

Topic: To study the wishes for future pregnancy management after an unexplained stillbirth.
Recruitment: A questionnaire at www.stillbirthsupport.org. Period: Apr 2006 – March 2007 (12 months). Final sample: 105.
Demographics: Mean age: 32.2; Country: Australia 46.7%, UK: 24.8%, USA/Can: 28.6%

Reference 18:

Topic: The investigation of different factors in relation to delayed conception (several publications).
Population: Women 18-40, resident of Denmark, in a stable relationship with a man, attempting to conceive <= 12 months, using no fertility treatment.
Recruitment: Questionnaire at study website. Advertisement on well-known health related website, press release on print media, online news sites, tv and radio. Recruitment period: from June 2007. Response: 2288 participants after 6 months, 3358 after a year, 5644 after 4 year.
Demographics: Country: Denmark.

Reference 19:

Topic: Changes in breast size before and directly after pregnancy in relation to infant's sex.

Population: Polish women who had at least one child.
Recruitment: Invitation were posted on three discussion-sites/ fora. Final sample: 120.
Demographics: Mean age: 30.9 (SD: 4.5); Country: Poland; First child: 57.5%.

Reference 20:

Topic: The presence of a premonition before the birth of stillborn baby and how this is dealt with.
Population: Women who had encountered a stillbirth >= 22 weeks pregnant.
Recruitment: A link to the questionnaire on the homepage of the Swedish National Infant Foundation; announcements in newspapers, on facebook and in a newsletter. Period: 27 March 2008 – 1 April 2010 (2 years). 1034 responses, final sample: 842.
Demographics: Country: Sweden; First child: 57%.

Reference 21:

Topic: The treatment decision making process for depressed women during pregnancy and after birth.
Population: Pregnant women or women who gave birth within the past year and were diagnosed with a major depressive disorder.
Recruitment: A link was placed on five websites about perinatal mood disorders. Period: April – Oct 2010 (7 months). 159 women began the survey, 125 completed it. Final sample: 100.
Demographics: Mean age: 31 (SD:5.0); Country: US?; College or graduate degree: 90%.

Reference 22:

Topic: To estimate end-of-season influenza vaccination coverage, knowledge, attitudes, and behaviors related to influenza vaccination among pregnant women.
Population: Women aged 18 - 49 years who were pregnant at any time during the peak influenza vaccination period (October 2010 - January 2011).
Recruitment: Eligible women were recruited from the Survey Spot panel operated by Survey Sampling International. Period: 4-25 April 2011 (22 days). Response: A total of 2,126 were determined to be pregnant any time since Aug 1 2010, and 1,937 (91%) completed the online survey, final sample: 1457.
Demographics: Country: US; College level or higher: 36.7%; White, non-hispanic: 67.1%.

Reference 23:

Topic: To estimate end-of-season influenza vaccination coverage, knowledge, attitudes, and behaviors related to influenza vaccination among pregnant women.
Population: Women aged 18 - 49 years who were pregnant at any time during the peak influenza vaccination period (October 2011 - January 2012).

Recruitment: Eligible women were recruited from the Survey Spot panel operated by Survey Sampling International. Period: April 3-17, 2012 (15 days). Response: A total of 2,223 were determined to be pregnant any time since Aug 1 2011, and 2,096 (94%) completed the online survey, final sample: 1660.
Demographics: Country: US; College level or higher: 49.1%; White, non-Hispanic: 71%.

Reference 24:

Topic: To estimate end-of-season influenza vaccination coverage, knowledge, attitudes, and behaviors related to influenza vaccination among pregnant women.
Population: Women aged 18 - 49 years who were pregnant since August 2012.
Recruitment: Eligible women were recruited from the Survey Spot panel operated by Survey Sampling International. Period: April 1-12, 2013 (13 days). Response: A total of 2,198 were determined to be eligible, and 2,047 (93%) completed the online survey, final sample: 1702.
Demographics: Country: US; College level or higher: 50.4%; White, non-Hispanic: 64.2%.

Reference 25:

Topic: To investigate patient acceptance of IVF practices.
Population: Patients undergoing fresh or cryopreserved/thawed embryo transfer in the academic hospital of the university of Iowa.
Recruitment: Patients were asked to complete an Internet-based survey during the 30-minute recovery period after ET at the clinic.
Total response rate: 98% (262/268).
Demographics: Mean age: 33 (SD:5); Country: US; College level or higher: 85%; White, non-Hispanic: 90%; First pregnancy: 40%.

Reference 26:

Topic: Maternally rated executive function in children exposed to nicotine during pregnancy.
Population: Mothers of children aged 5–18 years.
Recruitment: Flyers on community boards throughout the Portland metro area, western Oregon, and western Washington. Links on craigslist.org as well as on message boards for parents. Final sample: 375.
Demographics: Mean age at birth: 25.7; Non-white: 11.2%.

Reference 27:

Topic: About the reporting and content of hotspots during birth experiences and factors related to increased likelihood of PTSD (posttraumatic stress syndrome).
Population: Women over 18 who had given birth and could read and write English.
Recruitment: Participants were recruited from Internet support groups and charity websites aimed at women who experienced difficult or traumatic births. Period: Jan-June 2008 (6 months). Final sample: 675.

Demographics: Mean age: 31.6 (19-66) (SD: 6.6); White European: 98.6%; primiparous: 53.4%.

Reference 28:

Topic: The acceptance and reasons to accept or refuse vaccination during pregnancy.
Population: A random sample of 14,529 women with a due date between Nov 2009 and May 2010, selected from the national register for prenatal screening around 12 weeks.
Recruitment: Women were invited to participate in an Internet survey by a letter. Period: Apr-July 2010 (4 months). Final sample: 3067 (21%) of 14529 invited women.
Demographics: Mean age: 32; Country: Netherlands; High education: 60%

Reference 29:

Topic: Whether pregnant women would agree to be induced based on age: over 35 years.
Population: Women who were currently pregnant or had a baby in the last five years.
Recruitment: Advertisement on www.mumsnet.com. Period: 24 hours. Final sample: 663.
Demographics: Age: 19-50; Pregnant: 18%

Reference 30:

Topic questionnaire: Health problems, medication use and information need during pregnancy.
Publication A: Perceived need for medicines information during pregnancy and the information sources used in different regions of the world.
Publication B: Adherence to medication for chronic disorders.
Publication C: Patterns of medication use in pregnancy.
Publication D: Herbal medicine use in pregnancy and characterization of users.
Publication E: The use of multiple information sources and the consequences of conflicting information.
Population: Pregnant women and breastfeeding women with a child less thant 1-year old.
A and E: Pregnant women and lactating women with a child less than 6 months (less than 25 weeks) were included; B: Only pregnant women with a chronic disorder were included. C and D: all.
Recruitment: Invitations to join the study were posted on 1–4 Internet websites used by pregnant women in participating regions around the world. Period: 2 months in each country. All the data were collected during the period of 1 Oct 2011 to 29 Feb 2012.
Total study population: 9459; A and E: sub-population: 7092. B: Total: 315; 210 using medications for their chronic disease.

Demographics: Birthing population was reflected quite well by the sample with respect to age, parity and smoking. On average the women in the study were higher educated.

Reference 31:

Topic: Publication A: Treatment benefits reported by former obstetric acupuncture patients.
Population: Patients of an acupuncture clinic, seen in the previous decade, who were treated in pregnancy, and who had a specific obstetric concern.
Recruitment: Former patients were contacted by e-mail or physical address. Of 265 former acupuncture patients, 137 (51.7%) completed the survey.
Demographics: Mean age: 34.4 (SD: 3.9); Country: US; Primiparous: 49.3%; White: 95.5%.

Reference 32:

Topic: The psychological experience of a pregnancy after a perinatal loss.
Population: Pregnant women with a previous experience of one or several perinatal losses.
Recruitment: Advertisements on websites and specialized Internet fora (French chat fora on pregnancy and/or perinatal death). Period: Jan - May 2008 (5 months).
Response: 88 respondents, also 8 respondents asked by midwifes.
Demographics: Mean age: 29.8 (SD: 4.0); Country: France (majority); Primiparous: 59%.

Reference 33:

Topic/population: The attitudes of women who recently experienced miscarriage participating in Internet fora.
Recruitment: A message was sent to several French-language fora dealing with maternity or medical issues regarding the research study. Period: 5 weeks. Final sample: 305.
Demographics: Mean age: 28.6 (SD: 4.5); Country: France: 90% Belgium: 21.7%; No children: 52%.

Reference 34:

Topic: Consumption-frequency of foods and supplements rich in nutrients beneficial to nervous system (NS) health during pregnancy and its association with post-partum depression.
Population: Mothers who had not previously suffered from postpartum psychosis, were currently not affected by PPD and had given birth between 2003 and 2008.
Recruitment: An e-mail announcement to parent–toddler related discussion groups in Austria and via snowball sampling. Period: 23 march – 10 april 2010 (19 days). 435 responses, final sample: 400.

Reference 35:

Topic: to evaluate dietary supplement use and its socioeconomic, lifestyle and dietary correlates among pregnant women participating in the French NutriNet-Santé cohort study.
Population: All women who entered the cohort before September 2012 and had completed the dietary supplement questionnaire while pregnant.
Recruitment: Adults (>=18 y) living in France and having access to the Internet are recruited via mass-media campaigns. Period: May 2009 – Sept 2012. Final sample: 903
Demographics: Mean age: 31.7 (SD: 4.1); Country: France; No children: 57.4%.

Publications investigating a methodological topic:

Reference 18:

Topic: the feasibility of recruiting a cohort via the Internet (2 publications).
Population: Women 18-40, resident of Denmark, in a stable relationship with a man, attempting to conceive <= 12 months, using no fertility treatment.
Recruitment: Questionnaire at study website. Advertisement on well-known health related website, press release on print media, online news sites, tv and radio. Period:from June 2007. Response: 2288 participants after 6 months, 3358 after a year, 5644 after 4 year.

Reference 36:

Topic: The right method to use for identifying the component of anxiety in the Edinburg Postnatal Depression scale.
Population: Recent mothers (infant < 12 months).
Recruitment: Questionnaire on a website about pregnancy and motherhood by a major nutrition company. Period: 3 weeks. 492 responses, final sample: 440.
Demographics: Mean age: 30.2 (SD: 4.5); 34.3% educated to college and 43.9% to university level; First-time mothers: 56.4%.

Reference 37:

Topic: To Assess the feasibility of using the Internet for recruitment of pregnant women and follow-up of their children.
Population: Pregnant women with knowledge of the Italian language and the use of Internet.
Recruitment: Poster at the main hospitals of Turin, leaflets enclosed to lab results and ultrasounds and distributed at pre-delivery classes. Period: July 2005 – Dec 2006 (18 months). 687 responses, final sample: 670.
Demographics: Mean age: 33.3 (SD: 3.8); Country: Italy; Graduate: 57.3%; First pregnancy: 61.5%.

Reference 38:

Comparison of the use of phone and Internet as first fase survey approach and the impact of follow-up mail. Subject questionnaire: falls at work during pregnancy.
Population: Women that gave birth in one of the 7 hospitals in a large mid-Western city in the US during the 8 weeks before they had been contacted and who were 20 years or older when giving birth.
Recruitment: All eligible mothers were sent a letter to invite them to complete an Internet survey, call the researchers or to be available for contact by phone.
Period: Dec 1999 – July 2000 (8 months). 506 of 6217 eligible women completed the Internet survey (8.1%).
Demographics: Mean age: 30.6;Country: US; 84.4% educated to college level.

Reference 39:

Topic: Validation of a newly developed measure of control and support during birth.
Population: Women who gave birth within the last 3 years.
Recruitment: Online questionnaire, advertised on UK websites (aiming at women with normal or women with traumatic births) and advertised by snowball e-mails.
Period: Somewhere 2004-2005. 427 responses, final sample: 402.
Demographics: Mean age: 31.1 (SD: 4.7); First baby: 61.3%.

Reference 40:

Topic: The use of an eHealth program among pregnant women.
Population: Participants of the eHealth program: pregnant women recruited by any of the 25 midwifes in Amsterdam.
Recruitment: Invitation by email. Period: March – Aug 2006 (6 months). Response: 163 of 376 participants (43.4%).
Demographics: Mean age all participants: 30 (SD:5);Country: Netherlands; High level of education: 66%; No Dutch ethnicity: 26%; First pregnancy: 65%.

Reference 41:

Topic: Comparison of information that is gained by Internet or by an interview Subject questionnaire: collecting data to create a risk profile for the mother/baby.
Population: Women who attended the outpatient clinics for preconception care or fertility at a hospital in Rotterdam.
Recruitment: Women were sent an information leaflet. Period: Dec 2004 – Jan 2006 (14 months). 159 responses out of 349 leaflets sent (46%), 106 completed the Internet questionnaire.
Demographics: Mean age: 32 (21-42); Country: Netherlands; Dutch ethnicity: 84%; 47% planning their first pregnancy.

Reference 42:

Topic: Developing a model for understanding predictors of nulliparas' delivery preferences.
Population: Nulliparous women aged 18–40, living in the US who, at the time of participation, were pregnant at 20 or fewer weeks' gestation and had no prior pregnancy > 13 weeks.
Recruitment: Advertisements on the social networking website Facebook. Period: from 16 March to 22 July 2011 (4 months). 5963 people visited the survey site, 1075 agreed to participate, final sample: 344.
Demographics: Mean age: 20.9 (SD: 4.0); Country: US; White: 77.4%; College degree or higher: 14.6%.

Reference 43:

Topic: testing a mid-range nursing theory developed specifically for women's healthcare choices, using decision-making about medication use in pregnancy for anxiety and/or depression.
Population: Women who were 18 years or older, able to read and understand English, pregnant and had made a decision in pregnancy regarding medication use for symptoms of anxiety and/or depression.
Recruitment: An advertisement for the study was placed on pregnancy-related websites or fora and social networking websites, predominantly from English speaking countries. Period: 3 months starting in early 2011. 173 attempted the online survey, final sample: 143.
Demographics: Age between25-34: 70%; Country: US: 74%, UK: 17%; White/caucasian: 95%; College degree or higher: 67%; First pregnancy: 38%.

Reference 44:

Topic: What women learned about preeclampsia in the context of prenatal care during their first pregnancy.
Population: Women who had their first child from 2000-2008.
Recruitment: A link on the preeclampsia foundation website. Period: March and April of 2008. Final sample: 754.
Demographics: Country: US; Postgraduate or university degree: 65%.

Publications investigating Internet use related to pregnancy and health:

Reference 45:

Topic: Why and how women use the Internet as health information source and how it effects decision making.
Population: Women being pregnant or having had a baby in the last year, who used Internet during pregnancy to seek health information, able to read and understand English.

Recruitment: Promotion of study at 23 international sites with general pregnancy information (33 sites were asked). Period: July – Sept 2006 (12 weeks).
Final sample: 613.
Demographics: Mean age: 29.3 (SD: 5.0); 24 countries, UK 34.4%, Australia 23.8%, US 16%; Tertiary diploma: 77.5%; Pregnant: 61.8%; First pregnancy: 54.6%.

Reference 46:

Topic: Internet use and expectation regarding web-based info in childbearing women with type 1 diabetes.
Population: Swedish-speaking women with type 1 DM who gave birth in a hospital in west-Sweden during 2007-2009.
Recruitment: 139 Eligible women were contacted by phone to ask for participation. A link to the questionnaire was then sent by email. Final sample: 105 (75.5%).
Demographics: Secundary school or University: 96.2%; First time mothers: 37.1%.

Reference 47:

Topic: Demographics, use, and perceptions of mothers using online pregnancy or infant loss groups.
Population: Women who had encountered a miscarriage or preferably a stillbirth.
Recruitment: 15 sites about pregnancy-loss (predominantly late pregnancy loss >22wks) agreed to post a link to the survey on a total of 18 message boards. Period: Nov 2008 – June 2009 (8-months). Final sample: 1006.
Demographics: Mean age: 32 (15-71); 18 countries: US 88%, Canada 5%, Europe: 3%; At least some college: 91%; White: 92%; Currently pregnant: 16%.

Appendix 6: Propositions presented to pregnant women completing the survey used in Chapter 4.3 to investigate their perceptions about the risks of their asthma and asthma medication for their infant.

Dutch: **In hoeverre bent u het eens met de volgende stellingen:**	Mee eens	Niet mee eens	Weet het niet
Lichte benauwdheid kan schadelijk zijn voor mijn baby.	O	O	O
Een astma-aanval kan schadelijk zijn voor mijn baby.	O	O	O
Astmamedicijnen kunnen schadelijk zijn voor mijn baby.	O	O	O
Ik heb duidelijke informatie gekregen van mijn behandelend arts over de risico's van mijn astma en mijn medicijnen voor mijn kind.	O	O	O
Ik heb zelf informatie gezocht over de risico's van mijn astma en mijn medicijnen voor mijn kind.	O	O	O
Informatie die ik vond en/of kreeg sprak elkaar soms tegen.	O	O	O
Ik heb me wel eens zorgen gemaakt over de juiste keuze wat betreft mijn medicatie voor de gezondheid van mijn baby.	O	O	O

English: **To what extend do you agree with the following propositions:**	Agree	Do not agree	Don't know
Slight dyspnoea can be harmful to my baby.	O	O	O
An asthma attack can be harmful to my baby.	O	O	O
Asthma medication can be harmful to my baby.	O	O	O
I received clear information from my doctor about the risks of my asthma and my asthma medication for my child.	O	O	O
I searched for information myself about the risks of my asthma and my asthma medication for my child.	O	O	O
The information I got or found was sometimes contradictory.	O	O	O
I have been worrying about the right choices for the health of my baby, concerning my asthma medication.	O	O	O

Summary

Due to extensive research, more and more is known about risk factors and subsequent preventive actions in pregnancy. Yet in spite of this increasing knowledge many risks are still unclear. Epidemiologic research provides a substantial contribution to healthy pregnancies. To be able to appoint negative or protective effects of health and lifestyle factors around pregnancy on the future health of the child, epidemiologic researchers ideally need complete and valid information about the widest possible range of pregnancy characteristics and detailed information on the outcome under investigation. These data can be obtained in various ways, either retro- or prospectively. Although retrospective data are often easier to obtain, prospective data collection directly from pregnant women has several other advantages. Traditionally data are collected by a pen-and-paper survey or by interview either face-to-face or by telephone. But ever since the Internet is emerging, researchers have been investigating its possibilities as a tool for data collection. To explore the possibilities of collecting information on medication use and other potential risk factors directly from pregnant women via the Internet, the PROTECT pregnancy study was set up.

This thesis aims to investigate the different methods of data collection of risk factors in pregnancy. In addition, several observational epidemiologic study designs were used to assess associations between risk factors and negative birth outcomes. The benefits and drawbacks of the use of the Internet for data collection are elaborated, along with those of more traditional methods. Direct data collection from the pregnant women themselves is compared to indirect data collection from existing databases like the IADB.nl pregnancy database, a pharmacy prescription database and EUROCAT NNL, a birth defect registry. This thesis focuses on the collection of data on medication use during pregnancy and the investigation of relations between the use of particular medications during pregnancy and several negative effects for the child. Besides evaluating folic acid as a supplement to promote the health of the baby we will also focus on asthma and the use of asthma medication during pregnancy as potential risk factors for the baby's health.

Following the General Introduction, Section 2 covers direct data collection via pen-and-paper questionnaires. After the establishment of the preventive effect of folic acid on the development of neural tube defects, folic acid supplementation before and during pregnancy was recommended in the Netherlands since the nineties of the 20th century. Since 1995, regular surveys have been carried out among pregnant women in the Northern Netherlands to evaluate the effects of the several campaigns to propagate this supplementation and its sustainability.

Chapter 2.1 describes the results of the 2009 survey into knowledge and use of folic acid. Of all respondents, 51.6% reported to have used an adequate dose of at least 400 mcg folic acid during the entire recommended period from 4 weeks before until 8 weeks after conception. Planned pregnancy, smoking, folic acid use during a former pregnancy and the number of previous children, were predicting factors for the recommended use of folic acid. The knowledge about folic acid declined and the use during the recommended period did not improve since the survey of 2005. Based on this survey we conclude that there is still room for improvement with respect to knowledge and actual use of folic acid before pregnancy, especially with younger, low-educated women. Counselling should include family planning and use of contraceptives. In chapter 2.2 we show the results of the survey conducted in 2014, especially focusing on the development in knowledge and use of folic acid throughout the years. The absence of an incentive for the participating practices and the involvement in other studies affected the response rate of the 2014 survey substantially compared to the earlier ones (49.7% against 75-94%). With a recommended folic acid use of 56.2% in 2014, folic acid supplementation around pregnancy has stabilized during the last decade in the Netherlands. Since almost 90% of participating women knew about folic acid before they got pregnant already, the question remains how and whether recommended folic acid supplementation can be increased substantially. Reimbursing preconception consultation by midwives or other health care workers might contribute to a better uptake of the folic acid supplementation advice.

In chapter 2.3 we evaluate the representativeness of The Healthy Pregnant data set, a Dutch non-malformed control group collected from two midwife practices to see if it is useful as a control-group for EUROCAT NNL. The Healthy Pregnant data set was not representative of the general pregnant population in the northern part of the Netherlands. Women from both low and high education levels were overrepresented. Mothers were more likely to have a body mass index >25 kg/m^2 or to smoke but were less likely to consume alcohol. Specifically, the exposure to (chronic) drugs was underestimated, possibly because women with a chronic condition are referred to second-line care on the basis of medical indication. In the absence of a representative non-malformed control group, a genetic disorder control group should be considered as an appropriate solution. When conducting a control group for epidemiological research to evaluate the effects of medication use in pregnancy on the development of birth defects, it is more important that exposures to drugs are representative than the fact that the control group consists of non-malformed pregnancy outcomes, especially considering that malformed controls (chromosomals) can reduce recall bias.

In section three of the thesis indirect data collection is elaborated and the studies in this section all use the IADB.nl or EUROCAT NNL database. In chapter 3.1, we use the IADB.nl pregnancy database to describe changes in prescriptions for asthma medications to patients around their pregnancy. We collected data over a study period of 1 year before pregnancy until 6 months after birth, and analysed data from pregnant women who received at least 1 prescription for asthma medication during the study period (n=2072), identifying all prescriptions of asthma medication and oral corticosteroids. The study showed a significant increase in prescriptions for asthma medications among pregnant women in the period from 2004 to 2009, compared to the period before 2004, especially for the relatively new long-acting bronchodilators and combination preparations. Despite their understanding of the importance of adequate asthma-control, many women stop their controller therapy when they become pregnant. We observed a significant decrease in prescription of asthma medications during the first trimester of pregnancy in the period from 2004 until 2009, especially for long-acting bronchodilators, usually prescribed for patients with more severe asthma. Discontinuation could lead to severe symptoms of respiratory distress, along with risk of maternal and neonatal complications. There is room for improvement in treating asthma in pregnant women, which could lead to better health and care for mothers and children.

As stated before, folic acid supplementation of at least 400 mcg a day, before and in the beginning of pregnancy is recommended to reduce the risk of having a child with a neural tube defect. Women using folic acid antagonists, like antiepileptic drugs, women at risk for developing anaemia and women who have developed anaemia may receive a prescription for high dose folic acid (5mg). Chapter 3.2 describes the results of our study investigating delivery of high dose folic acid during pregnancy and the association with the use of asthma medication in the offspring, using the IADB.nl pregnancy database, since folic acid supplementation taken during pregnancy has been associated with an increased risk for childhood asthma. Delivery of asthma medication in children exposed in utero to high dose folic acid was compared to children who were not exposed to this high dose. High dose folic acid was dispensed in almost 3% of pregnancies, increasing with the course of pregnancy, especially with multiple pregnancies. The risk for asthma medication after exposure to maternal high dose folic acid during pregnancy increased up to 26% for the recurrent prescription of inhalation corticosteroids. Timing of folic acid use during pregnancy did not seem to have a significant effect on the associations studied. Additional research based on other data sources is recommended to confirm the association found.

After consumption, folic acid is metabolized by dihydrofolate reductase (DHFR) to its bioactive form 5-methyltetrahydrofolate (5-MTHF) that acts as a methyl-acceptor or -donor in biochemical reactions in the fetus, that are important for normal development. This folate metabolism can be disturbed by several drugs.

In chapter 3.3 we describe the results of case-control study investigating any increased risk on the development of folic acid sensitive birth defects after first trimester exposure to folic acid antagonists using the EUROCAT NNL database and the effect of concomitant intake of folic acid supplementation. We did not find an increased risk for folic acid sensitive birth defects after first trimester use of a folic acid antagonist. Investigating the several subgroups of births defects, an Odds Ratio >1 was only found for first trimester use of antiepileptic drugs and the occurrence of neural tube defects. We did not find a significant protective effect of the use of folic acid supplementation when using a folic acid antagonist during the first trimester of pregnancy. For risk assessment studies looking at birth defects, and especially birth defects that are rare, acquiring an adequate number of cases, is a challenge. For many of the associations studied, the numbers were too low to calculate Odds Ratios or to draw conclusions.

In Chapter 3.4, the IADB.nl pregnancy database and EUROCAT NNL are combined to see whether a comparison of drug use rates from the birth defect registry EUROCAT NNL (cases) with prescription rates from the population-based prescription database IADB.nl, (population), could be used to detect signals of teratogenic risk of drugs. We show that a case-population study is a suitable method for detecting signals of possible teratogenicity, provided that the teratogenic effects and drugs under study are as specific as possible and the drugs are widely used.

Section four describes data collection in pregnancy using web-based questionnaires. Chapter 4.1 shows the results of a systematic review investigating the use of web-based surveys examining a pregnancy-related topic. The literature search resulted in a sample of 37 eligible publications published from 2000 to 2013 collecting data for epidemiologic research from women who wanted to get pregnant, were pregnant or had been pregnant, by using an online questionnaire. As Internet use is increasing over time so were the number of publications we found per year. For the assessment of associations between exposure during pregnancy and pregnancy outcome, data collected should be complete and valid. We found no evidence of self-reported web-based data being more prone to incompleteness or non-validity than the same data collected via traditional methods like pen-and-paper, telephone surveys or interviews. When data could be compared to results from recent literature using other methods of data collection, results largely corresponded but completeness and validity are hard to judge because often no gold standard or other data sources are available, especially when perception is investigated. Due to possible selectivity of the sample, data obtained via open recruitment on the Internet is less suitable to calculate prevalences, but literature shows that web-responders do compare to responders by paper on most demographic variables when the same recruitment method is used.

To evaluate the potential contribution of collecting information on medication use and other potential risk factors directly from pregnant women via the Internet for research purposes, the PROTECT pregnancy study was started. In this non-interventional, prospective study ran in 4 European countries, pregnant women were asked to provide information about their health, lifestyle factors and medication use in their current pregnancy via a web-based questionnaire. In chapter 4.2 we investigate whether a database like the PROTECT pregnancy study can be used to explore potential relationships between lifestyle factors and birth outcomes. Lifestyle factors and birth outcomes reported by the women participating in PROTECT are compared to data from the general pregnant population of the participating countries or found in literature. The PROTECT pregnancy study recruited a selected population and characteristics investigated varied highly between the participating countries. Women participating in PROTECT were at average older, more highly educated and more health-focused. PROTECT participants also planned their pregnancy more often and generally took more folic acid supplements and multivitamins. Medication for different chronic conditions were also used more often, except for diabetes. The composition of the study sample will be determined by Internet access of the target population but Internet access hardly is a restricting factor in Western countries nowadays. The lack of population data as a gold standard and the diversity of data found in literature shows the difficulty of establishing the validity of lifestyle data reported. We found no conclusive evidence however to undervalue the validity and completeness of self-reported Internet-derived data compared to data obtained via traditional survey methods or derived from health care workers or medical databases, except for data on birth defects.

In chapter 4.3 a web-based survey is used to investigate the perceptions of pregnant women about the risks of their asthma and asthma medication for their offspring. Pregnant women with asthma were asked to provide information about asthma control and management before and during pregnancy and about the information they got on risk of asthma and asthma medication for the unborn child. In spite of guidelines advising the opposite, our study shows that still many women are advised by their physician to stop or change their current asthma medication when planning a pregnancy or after pregnancy is identified, leading to an increase in asthma symptoms for more than half of them. In line with chapter 3.1, generally relatively new medications containing a long-acting bronchodilator for maintenance of more severe asthma were stopped or changed to the older plain inhalation corticosteroids with substantial risk of the asthma getting less well controlled with consequent risks for the infant. Many women have their worries about possible risks of their asthma and their asthma medications and perceive a lack of support and guidance. Almost one third of the respondents indicated that the information they got or found was inconsistent.

In the field of asthma management during pregnancy there is still a lot to gain. Despite sufficient knowledge, latest guidelines are often not being followed. Healthcare providers need to be educated about the practical implementation of their knowledge about the importance of adequate asthma control in pregnancy.

Finally, we conclude that several factors have their influence on recruitment of participants for epidemiologic research and on the size and composition of the survey sample, and the different methods of data collection all have their opportunities and drawbacks, including new methodology like collecting data via the Internet.

Samenvatting

Door intensief onderzoek krijgen we steeds meer kennis over risicofactoren en het voorkomen hiervan tijdens de zwangerschap. Maar ondanks voortschrijdend inzicht is er nog veel onbekend. Epidemiologisch onderzoek levert een aanzienlijke bijdrage aan de toekomstige gezondheid van het kind. Onderzoekers willen graag complete en juiste informatie over zo veel mogelijke zwangerschapskenmerken en over de uitkomst die onderzocht wordt om negatieve of positieve factoren aan te kunnen tonen. Deze gegevens kunnen op verschillende manieren verkregen worden, zowel retro- als prospectief. Retrospectieve data zijn vaak makkelijker te verkrijgen, maar het verzamelen van prospectieve data van zwangere vrouwen zelf heeft verscheidene andere voordelen. Van oudsher worden deze gegevens verzameld met behulp van papieren vragenlijsten, telefoon of via interviews. Sinds de opkomst van het internet onderzoekt men de mogelijkheden van dit medium voor dataverzameling ten behoeve van wetenschappelijk onderzoek. Zo is het PROTECT zwangerschaps-onderzoek opgezet om te kijken naar de mogelijkheden van het verzamelen van informatie over medicijngebruik en andere mogelijke risicofactoren rechtstreeks van zwangere vrouwen zelf, via internet.

Dit proefschrift onderzoekt de verschillende methoden voor het verzamelen van informatie over risicofactoren tijdens de zwangerschap. Daarnaast worden verschillende observationele epidemiologische onderzoeksmethodes gebruikt om relaties aan te tonen tussen bepaalde risicofactoren en negatieve zwangerschapsuitkomsten. De voor- en nadelen van het gebruik van internet voor het verzamelen van informatie worden beschreven, naast die van de traditionele methodes. Dataverzameling van zwangere vrouwen zelf wordt vergeleken met indirecte dataverzameling vanuit bestaande databases zoals de IADB.nl, een database met informatie over afgeleverde geneesmiddelen in openbare apotheken in Nederland, en EUROCAT NNL, een registratie van aangeboren afwijkingen. De focus ligt bij het verzamelen van gegevens over medicijngebruik tijdens de zwangerschap en het bestuderen van eventuele relaties tussen het gebruik van bepaalde medicijnen en mogelijke negatieve gevolgen voor het kind. Speerpunten van dit proefschrift zijn het gebruik van foliumzuur als supplement ter bevordering van de gezondheid van de baby en astma en astmamedicatie tijdens de zwangerschap als mogelijke risicofactoren voor de gezondheid van het kind.

Na de algemene introductie behandelt deel 2 van dit proefschrift dataverzameling via papieren vragenlijsten. Nadat was aangetoond dat foliumzuur neurale buis defecten helpt voorkomen, adviseert men sinds de jaren 90 van de 20^{e} eeuw in Nederland om voor en in het begin van de zwangerschap een foliumzuursupplement in te nemen.

Sinds 1995 zijn er verschillende enquêtes gehouden onder zwangere vrouwen in Noord-Nederland naar de effecten van de campagnes ter promotie van foliumzuurgebruik en in hoeverre dit beklijft. Hoofdstuk 2.1 beschrijft de resultaten van de enquête uit 2009 naar de kennis over en het gebruik van foliumzuur. De helft (51.6%) van de respondenten gaf aan de aanbevolen dosis foliumzuur van ten minste 400 mcg te hebben genomen vanaf 4 weken voor tot en met 8 weken na de conceptie. Het plannen van de zwangerschap, roken, foliumzuurgebruik tijdens een eerdere zwangerschap en het aantal eerdere kinderen waren voorspellende factoren voor het juist gebruik van foliumzuur. Kennis over foliumzuur nam af en juist gebruik steeg niet ten opzichte van de vorige enquête uit 2005. Geconcludeerd kan worden dat de kennis over foliumzuur en het op tijd beginnen met innemen beter kan, voornamelijk bij jongere, lager opgeleide vrouwen. Voorlichting zou zich ook moeten richten op gezinsplanning en het gebruik van anticonceptie. Hoofdstuk 2.2 laat de resultaten zien van de enquête uit 2014. Hierbij kijken we vooral naar de ontwikkeling van de kennis over foliumzuur en het foliumzuurgebruik in de afgelopen jaren. Deze keer konden we de deelnemende praktijken geen vergoeding geven voor hun deelname, zoals bij voorgaande enquêtes wel het geval was. Dit had een duidelijk effect op de respons (49.7% tegen 75-94%). Met een correct gebruik van 56.2% in 2014, heeft het foliumzuurgebruik in Nederland rondom de zwangerschap zich de laatste 10 jaar gestabiliseerd. Bijna 90% van de deelnemende vrouwen heeft al voor de zwangerschap gehoord over foliumzuur, wat de vraag oproept hoe en tot welk percentage het foliumzuurgebruik nog verbeterd kan worden. Vergoeding van preconceptieconsulten bij verloskundigen of andere gezondheidswerkers zou kunnen bijdragen aan een betere uitvoering van de bestaande adviezen en een tijdig starten met foliumzuur.

In hoofdstuk 2.3 wordt gekeken naar de representativiteit van Gezond Zwanger, een controlegroep die gebruikt zou kunnen worden voor EUROCAT NNL, bestaande uit kinderen zonder aangeboren afwijkingen verzameld met behulp van twee verloskundigenpraktijken in Noord Nederland. Deelneemsters aan Gezond zwanger waren niet representatief voor de algemene zwangere populatie in de regio. Hoger en lager opgeleide vrouwen waren oververtegenwoordigd en er waren meer moeders met een BMI > 25 kg/m2, en meer moeders die rookten en die alcohol gebruikten. Vooral het (chronisch) medicijngebruik tijdens de zwangerschap was laag, waarschijnlijk omdat vrouwen met een chronische ziekte vaak naar de tweedelijns zwangerschapszorg worden verwezen. Bij het samenstellen van een controlegroep voor epidemiologisch onderzoek naar de effecten van medicijngebruik tijdens de zwangerschap op het ontstaan van aangeboren afwijkingen is het belangrijk dat de blootstelling aan de medicijnen representatief is.

Deel 3 van dit proefschrift behandelt indirecte dataverzameling en de studies in dit deel gebruiken allemaal de IADB.nl of EUROCAT NNL. Hoofdstuk 3.1 beschrijft de veranderingen in voorgeschreven astmamedicatie rondom de zwangerschap m.b.v. de IADB.nl zwangerschapsdatabase. We identificeerden 2072 zwangerschappen met een voorschrift voor astmamedicijnen vanaf 1 jaar voor de zwangerschap tot een half jaar na de geboorte en registreerden alle astmamedicatie en orale corticosteroïden. Vergeleken met de periode voor 2004 was er in 2004-2009 een significante stijging van het aantal voorschriften voor astmamedicijnen tijdens de zwangerschap, voornamelijk voor de relatief nieuwe langwerkende luchtwegverwijders en combinatiepreparaten. Er zijn nog steeds veel vrouwen die stoppen met hun onderhoudsmedicatie wanneer ze zwanger zijn, ondanks toegenomen aandacht voor het belang van goede astmacontrole tijdens de zwangerschap. In 2004-2009 zagen we een significante daling van het aantal voorschriften voor astmamedicatie in het eerste zwangerschapstrimester, voornamelijk voor langwerkende luchtwegverwijders die meestal worden voorgeschreven wanneer de astma moeilijk te behandelen is. Het stoppen met deze medicijnen kan leiden tot ernstige benauwdheidsklachten die gepaard gaan met risico's op maternale en neonatale complicaties. Er is ruimte voor verbetering als het gaat om de behandeling van astma bij zwangere vrouwen. Dit kan leiden tot een betere gezondheid en zorg voor zowel de moeder als het ongeboren kind.

Zoals eerder aangegeven wordt het innemen van ten minste 400 mcg foliumzuur per dag voor en in het begin van de zwangerschap aanbevolen om het risico op een neuraal buisdefect bij het kindje te verlagen. Aan vrouwen die een foliumzuurantagonist gebruiken, bijvoorbeeld een anti-epilepticum, vrouwen met een verhoogd risico op anemie en vrouwen die anemie hebben ontwikkeld tijdens de zwangerschap wordt soms een veel hogere dosis foliumzuur voorgeschreven (5 mg). Foliumzuurgebruik tijdens de zwangerschap wordt echter ook geassocieerd met een verhoogd risico op het ontwikkelen van astma bij het kind. Hoofdstuk 3.2 beschrijft de resultaten van een studie naar het afleveren van hoge dosis foliumzuur tijdens de zwangerschap en de relatie met het gebruik van astmamedicatie bij de kinderen en maakt hiervoor gebruik van de IADB.nl zwangerschapsdatabase. De afgifte van astmamedicijnen aan kinderen die tijdens de zwangerschap zijn blootgesteld aan een hoge dosis foliumzuur is vergeleken met dat aan kinderen die niet aan deze hoge dosis zijn blootgesteld. In bijna 3% van de zwangerschappen was er sprake van afgifte van hoge dosis foliumzuur. Dit percentage nam toe met het verloop van de zwangerschap waarbij het voornamelijk ging om tweelingzwangerschappen. Na blootstelling aan hoge dosis foliumzuur in de zwangerschap was er een tot 26% hoger risico voor herhaaldelijke afgifte van inhalatiecorticosteroïden. De zwangerschapsperiode waarin het foliumzuur was voorgeschreven leek hier verder niet van invloed op te zijn. Aanvullend onderzoek met gebruik van andere gegevensbronnen word aangeraden om de gevonden relatie te bevestigen.

Na inname wordt foliumzuur omgezet door dihydrofolaat reductase (DHFR) in de bioactieve component 5-metylhydrofolaat (5-MTHF) dat dient als een metyl-acceptor of -donor in biochemische reacties bij de foetus die belangrijk zijn voor de normale ontwikkeling. Dit mechanisme kan worden verstoort door verschillende medicijnen. In hoofdstuk 3.3 worden de resultaten beschreven van een case-control studie naar een verhoogd risico op het ontwikkelen van foliumzuurgevoelige aangeboren afwijkingen na blootstelling in het eerste trimester van de zwangerschap aan foliumzuurantagonisten en het effect van gelijktijdige inname van foliumzuur. Hiervoor gebruiken we de EUROCAT NNL database. We vonden geen verhoogd risico op foliumzuurgevoelige aangeboren afwijkingen na blootstelling aan foliumzuurantagonisten. Wanneer we keken naar verschillende subgroepen van afwijkingen vonden we alleen een verhoogd risico (Odds Ratio >1) voor neurale buisdefecten na het gebruik van anti-epileptica. Een beschermend effect van het gebruik van foliumzuur bij het gebruik van foliumzuurantagonisten tijdens het eerste trimester van de zwangerschap kon niet worden aangetoond. Het blijft een uitdaging om bij risicostudies naar aangeboren afwijkingen voldoende cases te verzamelen, voornamelijk als het gaat om afwijkingen die niet zo vaak voorkomen. Voor veel van de associaties die we hebben bestudeerd hadden we te weinig cases om een relatie (Odds Ratio) te berekenen of een concluderende uitspraak te kunnen doen.

In hoofdstuk 3.4 worden de IADB.nl en EUROCAT NNL gecombineerd. Gekeken wordt of data over medicijngebruik uit EUROCAT NNL, een registratie van aangeboren afwijkingen (cases) kan worden vergeleken met apotheekdata uit de IADB.nl (populatie) om mogelijke teratogeniteit te signaleren. Deze studie laat zien dat een case-populatie studie een passende methode is voor het detecteren van signalen over mogelijke teratogeniteit wanneer de te onderzoeken teratogene effecten en medicijnen zo specifiek mogelijk zijn en de medicijnen vrij algemeen gebruikt worden.

Deel 4 van dit proefschrift beschrijft dataverzameling tijdens de zwangerschap met behulp van online vragenlijsten. Hoofdstuk 4.1 laat de resultaten zien van een systematisch review naar het gebruik van online enquêtes naar een zwangerschaps-gerelateerd onderwerp. Literatuuronderzoek resulteerde in een set van 37 geschikte publicaties van 2000 – 2013 waarin met behulp van online vragenlijsten gegevens werden verzameld voor epidemiologisch onderzoek van vrouwen die zwanger wilden worden, zwanger waren of waren geweest. Parallel aan het internetgebruik steeg ook het aantal geschikte publicaties per jaar gedurende de onderzochte periode. Voor het aantonen van de effecten van blootstelling tijdens de zwangerschap is complete en valide data nodig over blootstelling en zwangerschapsuitkomst. Informatie online verzameld via zelfrapportage is niet aantoonbaar gevoeliger voor onjuistheid of onvolledigheid dan dezelfde data verzameld via traditionele methodes zoals papieren vragenlijsten, telefoon of interviews.

Waar data vergeleken konden worden met recente literatuur waar gebruik werd gemaakt van andere methodes voor het verkrijgen van de benodigde gegevens, was er een grote mate van overeenkomst. Volledigheid en validiteit is echter moeilijk te beoordelen omdat er vaak geen gouden standaard of andere databronnen voorhanden zijn, vooral wanneer het gaat om het onderzoeken van percepties. Bij open werving via internet is er een grote kans op selectiviteit van de steekproef, hierdoor is de verkregen data minder geschikt voor het berekenen van prevalenties. Literatuur laat echter zien dat wanneer dezelfde wervingsmethode wordt gebruikt, respondenten via internet vergelijkbaar zijn met respondenten via papieren vragenlijsten met betrekking tot de meeste demografische variabelen.

Het PROTECT zwangerschapsonderzoek is opgezet om te bestuderen in hoeverre informatie over medicijngebruik en andere mogelijke risicofactoren, verzameld door middel van zelfrapportage door zwangere vrouwen via internet, kan bijdragen aan wetenschappelijk onderzoek. In deze prospectieve studie zonder interventie, uitgevoerd in 4 Europese landen werden zwangere vrouwen gevraagd om informatie te geven over hun gezondheid, levensstijl en medicijngebruik tijdens hun huidige zwangerschap via een online vragenlijst. In hoofdstuk 4.2 wordt onderzocht of een database zoals het PROTECT zwangerschapsonderzoek gebruikt kan worden om mogelijke relaties te onderzoeken tussen levensstijlfactoren en zwangerschapsuitkomst. De door de deelneemsters gerapporteerde levensstijl-factoren en zwangerschapsuitkomsten worden vergeleken met data van de algemene zwangere populatie van de deelnemende landen of met data uit de literatuur. Het PROTECT zwangerschapsonderzoek heeft een selectieve populatie zwangere vrouwen gerekruteerd en de onderzochte variabelen verschilden veel tussen de deelnemende landen. PROTECT deelneemsters waren over het algemeen ouder, hoger opgeleid en meer gericht op hun gezondheid. Ook waren de zwangerschappen vaker gepland en werd er vaker foliumzuur en multivitaminen geslikt. Medicijnen voor chronische aandoeningen werden ook vaker gebruikt, behalve voor diabetes. De opbouw van de studiepopulatie wordt onder andere bepaald door internettoegang van de doelpopulatie, maar internettoegang is anno 2013 amper meer een beperkende factor in het Westen. Het ontbreken van algemene data als gouden standaard en de grote verschillen die we vonden in de literatuur geven aan hoe moeilijk het is om de validiteit van de verkregen data te bepalen. We vonden echter geen duidelijk bewijs dat de validiteit en volledigheid van data verkregen door middel van zelfrapportage via internet onderdoet voor die van data verkregen via traditionele enquête methodes of via gezondheidswerkers of medische databases, behalve wanneer het gaat om informatie over aangeboren afwijkingen.

In hoofdstuk 4.3 gebruiken we een online vragenlijst om te onderzoeken hoe zwangere vrouwen de risico's van hun astma en astmamedicijnen voor hun kind beleven. We vroegen zwangere vrouwen met astma om informatie te verstrekken over de mate van astmacontrole en behandeling voor en tijdens de zwangerschap en over de informatie die ze hebben gekregen over de risico's van astma en astmamedicatie voor het ongeboren kind. Het onderzoek laat zien dat vrouwen nog steeds vaak door hun behandelend arts worden geadviseerd om hun huidige astmamedicatie te stoppen of te wijzigen wanneer ze zwanger willen worden of als ze zwanger zijn, ondanks dat de richtlijnen dit juist niet adviseren. In meer dan de helft van de gevallen leidt dit tot een toename van de astmaklachten. In lijn met hoofdstuk 3.1 werden vooral de relatief nieuwe onderhoudsmedicijnen met een langwerkende luchtwegverwijder, vaak gebruikt bij ernstiger astma, gestopt of omgezet naar de oudere enkelvoudige inhalatie corticosteroïden. Dit geeft een substantieel risico op een toename van de klachten met navenante risico's voor de baby. Veel vrouwen maken zich zorgen over de mogelijke risico's van hun astma en astmamedicatie en ervaren een gebrek aan steun en begeleiding. Bijna een derde van de respondenten geeft aan dat de informatie die ze hebben gezocht of gekregen inconsistent was. Op het gebied van astmamanagement tijdens de zwangerschap kan nog veel verbeterd worden. Ondanks voldoende kennis worden de meest recente richtlijnen vaak nog niet gevolgd. Gezondheidswerkers zouden beter onderricht moeten worden over de praktische uitwerking van hun kennis over het belang van een adequate astmacontrole tijdens de zwangerschap.

Tenslotte kunnen we concluderen dat er verschillende factoren van invloed zijn op de werving van deelnemers voor epidemiologisch onderzoek en op de grootte en samenstelling van de steekproef. De verschillende methodes hebben allemaal hun voor- en nadelen, dit geldt ook voor nieuwe methodes zoals het verzamelen van gegevens via internet.

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